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MARY DEVLIN CAPIZZI
202-408-7101

September 30, 1999

BY COURIER

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 99D-1738

Dear Sir or Madam:

Please find enclosed two originals and one copy of the comments of The International Pharmaceutical Aerosol Consortium ("IPAC") on the FDA's draft *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action,* dated June 1999 (the "Draft Guidance"). Please file the original copies and time/date stamp the photocopy and return it to the messenger.

We greatly appreciate the Agency's flexibility in allowing us extra time to review and comment on the Draft Guidance (as discussed via email on August 26, 1999 with Dr. Wallace Adams, Office of Pharmaceutical Science, CDER/FDA).

Thank you for your consideration.

Sincerely,

Mary Devlin Capizzi

Mary Devlin Capizzi

Enclosure

99D-1738

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COMMENTS

on a draft Guidance for Industry
Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action

Submitted by
The International Pharmaceutical Aerosol Consortium

September 30, 1999

I. INTRODUCTION

The International Pharmaceutical Aerosol Consortium (IPAC) is an association of companies that develop and manufacture oral inhalation and intranasal products for local and systemic treatment of chronic obstructive pulmonary disease (COPD), rhinitis, and migraine. These comments are being submitted on behalf of the following members of IPAC's Working Group on FDA Guidance: Aradigm, AstraZeneca, Boehringer Ingelheim, Dura Pharmaceuticals, Eli Lilly, GlaxoWellcome, Inhale Therapeutic Systems, Inc., Medeva Americas, Pfizer, Rhône-Poulenc Rorer, Schering-Plough Corporation and 3M Pharmaceuticals. The members of the IPAC Working Group on FDA Guidance are committed to the highest standards of safety, efficacy and quality in the development and manufacture of drug products for oral inhalation and intranasal delivery.

The member companies of the IPAC Working Group on FDA Guidance commend the Oral Inhalation and Nasal Drug Products Technical Committee, the Locally Acting Drug Products Steering Committee, the Biopharmaceutics Coordinating Committee and the Inhalation Drug Products Working Group of the Chemistry, Manufacturing, and Controls Coordinating Committee, in the Center for Drug Evaluation and Research (CDER), on their efforts to develop this Draft Guidance for Industry. The IPAC Working Group also appreciates the opportunity to provide the following comments to the Agency.

Patients rely on nasal spray medications and inhalation solutions and suspensions for the safe and effective treatment of diseases. The Food and Drug Administration (FDA) and the pharmaceutical industry each strive to respond to the needs of patients for these medications by expediting the availability of new products while maintaining appropriate standards of safety, efficacy and quality. We hope that through our comments we may assist the Agency in developing a final Guidance that will assist developers in measuring bioavailability (BA) and establishing bioequivalence (BE) in support of new or abbreviated drug applications for locally acting drugs in nasal aerosols and nasal sprays.

II. GENERAL COMMENTS

- We are encouraged that the Draft Guidance recognizes the challenges and difficulties of demonstrating equivalence of nasal sprays and inhalation therapies, particularly of corticosteroids intended for local action.

- We strongly support application of the same standards to ANDAs and NDAs, as product quality, safety and efficacy considerations are independent of the regulatory mechanism for approval.

- We agree that systemic pharmacokinetic (PK) and pharmacodynamic (PD) data alone are not sufficient to determine bioequivalence for nasal solution and suspension drug products that are locally acting.

- We agree that test products should be qualitatively (Q1) the same and quantitatively (Q2) essentially the same as the reference product, and that test products should mirror the container closure system of the reference product.

- We recommend that requirements for in vivo and in vitro testing for BE approval of all nasal products be the same and include in vitro pharmaceutical equivalence, systemic exposure and local delivery.

- In light of the expected revisions to 21 CFR 314.70, we believe that the Postapproval Change section is beyond the scope of this Draft Guidance and should be deleted.

- We note that the Draft Guidance does not provide guidance on in vivo bioequivalence standards, and therefore a second version of the Draft Guidance should be reissued, with another opportunity for public comment when such guidance is available.

III. BA/BE TESTING OF NASAL SOLUTION PRODUCTS SHOULD INCLUDE IN VIVO MEASUREMENTS

The Draft Guidance relies on in vitro methods only for BA and BE testing of locally acting solution nasal drug products. The Draft Guidance notes the questionable clinical relevance of in vitro methods, but nevertheless recommends exclusive reliance on in vitro methods to access BA and BE in nasal solution drug products. We believe that the Draft Guidance includes a number of erroneous assumptions upon which it relies in drawing its conclusion that exclusive reliance on vitro methods is sufficient. Following are two examples of such assumptions:

- ***Assumption: "Equivalent in vitro performance assures bioequivalence."***

  To base the entire BE approval of any nasal solution product solely upon in vitro criteria is flawed unless there is sufficient in vivo correlation to establish the predictability and objectivity of the tests. Clinical relevance of the proposed in vitro tests for nasal products has not yet been established. A major concern with relying upon in vitro data as the sole basis for any BE assessment is the lack of objectivity of the in vitro tests.

- ***Assumption: "In vitro studies would be more sensitive than clinical studies."***

  This assumption ignores the ability to perform BE pharmacokinetic studies on nasal corticosteroid products, including budesonide, flunisolide, and triamcinolone acetonide. There is no apparent reason why well-designed pharmacokinetic and pharmacodynamic studies should be attributed less weight than in vitro experiments. Similarly, there is no apparent reason why a well-designed clinical study for local delivery, such as a clinical trial with both placebo and active treatment reference product controls, should be given less weight than in vitro experiments.

Given that there is no scientific basis to conclude that the current in vitro tests are *a priori* more sensitive BE measures than clinical trials and that these in vitro tests are adequate to produce quality BA and BE results for nasal solution products, we propose that a scientifically justifiable BE/BA testing program be applied to both nasal solution and suspension formulations. In particular, we propose that:

- product quality BA and BE testing program include:

  1) the in vitro methods included in the Draft Guidance,

2) the systemic exposure study, and
3) the local delivery study;

- all three types of testing be required of all nasal products, and not just suspension products; and

- approval criteria would require that statistical BE tests be met for all three analyses.

The improvements suggested above would resolve the inconsistencies in the Draft Guidance and provide fair and objective approval criteria for all nasal products.

IV. IN VITRO TESTS

In Vitro Measurements Must be Appropriate and Clinically Relevant

The in vitro aspects of the Draft Guidance are in a relatively advanced state of development compared to the in vivo sections of the document, however, there is no evidence that the in vitro measures selected are appropriate and clinically relevant. This gives cause for concern should these requirements become mandatory for characterizing and demonstrating equivalence of innovator or generic products subject to minor manufacturing changes.

Equivalence of the Container and Closure System

The container and closure system is an intimate part of the dose form and influences how much drug will be delivered and where drug will be delivered. The Draft Guidance should therefore specifically require equivalence of all critical dimensions of the container and closure system of the test and reference products.

Reliance Upon In Vitro PSD Methods

The Draft Guidance assumes that in vitro PSD methods can measure product quality BA and BE and are more sensitive and discriminating than in vivo methods. Compared to in vitro methods, clinical endpoints may be more variable and relatively insensitive in detecting differences between products; however, this observation alone is insufficient to justify reliance upon even more problematic in vitro methods. For example:

- Available PSD test methods for nasal products have significant shortcomings as BA and BE metrics. The "throats" or inlet of the preferred Multistage Cascade Impaction (CI) and the Multistage Liquid Impinger (MSLI) in vitro PSD tests have been developed for oral inhalation products and bear no relationship to the anatomy of the nose. The test inlet flow velocity has also been developed for oral inhalation products; however, this velocity is different for products given to the nose.

- The stages selected for the PSD analysis are appropriate for oral inhalation, but these particle-sizing stages have not been optimized for nasal delivery. Current data indicates that larger sized particles, greater than 10 microns, are preferable for nasal bioactivity. As acknowledged on page 13 of the Draft Guidance, this is precisely the size range where the available CI and MSLI in vitro tests are the least precise and the least useful, as these tests do not size particles greater than 10 microns.

Batch Requirements in the Draft Guidance are Inappropriate

Section A on page 8 of the Draft Guidance, which pertains to batches and drug product sample collection, contains batch requirements that are inappropriate for a product quality BE assessment. Because of the critical nature of this testing in the BE assessment, and because of the limited number (three) of batches examined, it is appropriate and fair to require three production-scale batches of the test product, as well as the reference product. If the stability tests or the clinical studies on the test product were done with smaller-sized lots, then these should be tested and included in the comparison as well. Batches should represent production scale and process, container closure system, and active drug substance.

Control of Extractables Should be Consistent for Test and Innovator Products

In light of the Agency's requirements for characterizing the impurities and extractables in the components of the container and closure system of the innovator product to ppm and ppb levels, extractables should be controlled in the components of the test product to the same levels. The requirements for controlling extractables in all components of the container and closure system should be specified in the Draft Guidance, precisely as they are specified in the *Draft Guidance For Industry: Metered Dose*

Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, Chemistry, Manufacturing and Controls.

V. LOCAL DELIVERY STUDIES

BE Assessments of Local Delivery

The Draft Guidance attempts to describe appropriate designs for local delivery studies. To facilitate BE assessments of local delivery, however, the Draft Guidance should provide more flexibility for the sponsor to choose the most appropriate study design. An appropriate BE study with a clinical endpoint to establish equivalent local delivery of drug from test and reference products to the nose should include documentation of the sensitivity of the study design in order to discriminate between differing doses. This documentation typically relies upon the inclusion of a second dose of the reference product and may also include a second dose of the test product. It is appropriate to allow doses to differ by as much as fourfold and to utilize doses outside of the recommended therapeutic range to increase study sensitivity.

To properly differentiate product-related findings from those occurring by chance, it is critical that a placebo treatment be included in any local delivery BE study. Such a trial, containing test and reference products and placebo, has recently been published for a test nasal formulation of beclomethasone dipropionate (*See* Casale TB, Azzam SM, Miller RE, Oren J (1999), *Demonstration of therapeutic equivalence of generic and innovator beclomethasone in seasonal allergic rhinitis*, SAR Study Group, *Ann Allergy Asthma J 82*: 435-441, (Study design had the sensitivity to conclude local delivery BE for the test and reference nasal products)).

BE Requirements for Local Delivery for Seasonal Allergic Rhinitis

The Draft Guidance proposes on page 18 that fulfilling the BE requirements for local delivery for seasonal allergic rhinitis (SAR) is sufficient to grant the sponsor of the test product all the indications in the reference product labeling. This proposal does not seem scientifically justifiable in light of the uncertainties of the particle size distributions of test and reference products. The test product might pass a SAR clinical test, yet would fail the second indication test if this were studied.

VI. STUDIES OF SYSTEMIC EXPOSURE AND SAFETY

Study Design Should be Sensitive to Differing Doses

An appropriate BE study with a pharmacokinetic or pharmacodynamic endpoint to establish equivalent systemic exposure of drug from test and reference products to the nose should include documentation of the sensitivity of the study design to discriminate between differing doses. This documentation typically relies upon the inclusion of a second dose of the reference product and may also include a second dose of a test product.

BE Standards Should be Clinically Relevant

We agree that PK and PD studies to assess the effects of a drug on HPA-axis should be performed and are helpful in characterizing the systemic exposure of locally active compounds. These studies, however, may not serve as adequate indicators to assess all of the potential systemic effects. We strongly support the appropriate use of the systemic study as one component of the BE assessment (other components are in vitro testing and local delivery study). It must be recognized that PK and PD testing alone are not sufficient to justify substitutability of one product for another.

The substitutability of products is of particular relevance to pediatric and geriatric patient populations, where the potential to effect growth velocity or fragile/broken bones, respectively, is magnified. The FDA, in its *Class Labeling for Intranasal and Orally Inhaled Corticosteroid Containing Drug Products*, acknowledges that a reduction in growth velocity in pediatric patients has been observed in the absence of laboratory evidence of HPA-axis suppression, and suggests that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. We believe that the Draft Guidance, in providing BE guidance for systemic exposure, should require validated study models to document equivalent systemic safety (especially if it is a pharmocodynamic model).

Pediatric Use of Drug Products Should be Considered

The Draft Guidance does not consider the required BE testing for nasal products administered to children. As it is well established that children metabolize and react to many drugs differently than adults, it is not appropriate to assume that BE results generated in adults apply equally well to children. For nasal products in particular, care must be exercised when extrapolating to the pediatric population because children

breathe at a different rate, have a different airflow, and potentially different nasal drug deposition because of the smaller size of the airway passages compared with adults. A proposed BE testing program in children, including at least a systemic exposure study for safety, is needed.

VII. THE GUIDANCE REQUIRES FURTHER DEVELOPMENT

Guidance on BE Statistical Standards Needed

The statistical requirements in the Draft Guidance, including the proposed upper limits for concluding BE for the in vitro, local delivery and systemic exposure assessments, are incomplete. In particular, no in vivo BE standards are provided. Section IX.E of the Draft Guidance, which is under development, is absent from the document. In addition, a significant portion of Section IX.B.2.b was not made available to industry until August 16, 1999. We strongly recommend that the Draft Guidance be reissued as a second draft when such statistical procedures and definitions are available, and a second period of public comment be required before this Draft Guidance may be finalized.

Consistency with Other Guidances

We recommend that a stronger link be created between the development tests described in the Draft Guidance and the in vitro tests described in the companion *Chemistry, Manufacturing and Controls (CMC) Draft Guidances For Industry: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products, and Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products.*

We also suggest that the Postapproval Change section be deleted from the Draft Guidance. In light of the collaborative process undertaken by industry and the Agency in developing the SUPAC guidances, and the expected revisions to 21 CFR 314.70, we believe a section addressing Postapproval Change is beyond the scope of this Draft Guidance.

VIII. CONCLUSION

We support the Agency's efforts to develop guidance on product quality BA and BE studies for nasal aerosols and nasal sprays and appreciate the Agency's openness to accept public comments on the current Draft Guidance. We also commend the Agency for initiating a discussion on BA and BE studies at the *AAPS/FDA/USP Workshop on*

Regulatory Issues Related to Drug Products for Oral Inhalation and Nasal Delivery, held on 3-4 June 1999 in Washington, D.C. We note, however, that since the *Draft Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* was first made available at the June Workshop, the Workshop did not provide the opportunity for meaningful review and discussion of the Draft Guidance. Further, the Draft Guidance, as currently published, is incomplete. The Draft Guidance does not provide guidance on in vivo bioequivalence standards, and must be revised to incorporate certain statistical procedures and definitions.

We believe that a second draft of the *Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* should be issued prior to finalization of the Guidance. We reiterate our position that the revised Draft Guidance should require that in vivo and in vitro testing for BE approval criteria of all nasal products be identical and include in vitro pharmaceutical equivalence, systemic exposure and local delivery.

We also suggest that the Agency utilize a technical process to assemble the best available medical, pharmaceutical and academic expertise, from within and outside the FDA, to further address BA and BE studies and make recommendations for a revised draft Guidance. We believe that such a technical process is critical to the future development of nasal sprays and nasal aerosols. We are strongly encouraged by the Agency's recent decision to create an expert panel that will evaluate further CMC and BA/BE issues, and we acknowledge that the creation of an expert panel may be a first step in a necessary technical process.

We hope our comments will be of value to the Agency and we look forward to the publication of a revised Draft Guidance that will effectively serve the current and future needs of the inhalation drug product industry.

MARY DEVLIN CAPIZZI
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July 31, 2000

BY OVERNIGHT DELIVERY AND VIA E-MAIL

Nancy Chamberlin
Executive Secretary and Advisory Consultants Staff
Center for Drug Evaluation and Research (HFD-21)
Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20857

Re: FDA's draft *Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation,* dated November 13, 1998; and FDA's draft *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation,* dated June 2, 1999

Dear Ms. Chamberlin:

On behalf of the ITFG/IPAC Collaboration, I am transmitting herewith the *Initial Assessment of the ITFG/IPAC Dose Content Uniformity (DCU) Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration.* This document, prepared by the DCU Working Group of the ITFG/IPAC Collaboration, constitutes part of the work described by the ITFG/IPAC Collaboration in its presentation to the Orally Inhaled and Nasal Drug Products (OINDP) Subcommittee on April 26 of this year. We ask that this initial assessment be posted on the FDA's website for the OINDP Subcommittee and circulated to interested persons at the FDA and the members and invited guests of the OINDP Subcommittee. We hope this report is of value to the Agency as it continues its work to finalize the Guidances, referred to above.

The initial assessment constitutes a first step in the analysis of the DCU database compiled by the ITFG/IPAC Collaboration. We believe that the database provides an important opportunity to investigate relationships between the DCU standards proposed in the Guidances and the capabilities of today's development and manufacturing technology. In the coming weeks, we will be finalizing our plan for this further investigation.

We would find it of great value to hear FDA's views on the results of our initial assessment as well as to discuss our plans for further detailed analysis. Accordingly, we would appreciate an opportunity to meet with appropriate representatives from the Agency prior to the execution of our detailed analysis plans so that this second phase of the data analysis meets the needs of all parties.

We anticipate that the details of our next steps will be finalized by mid-September and would like to suggest that a meeting be scheduled at this time for the latter part of September. We would plan to send the Agency our plans for follow-up work prior to the meeting to give the Agency adequate review time prior to the meeting.

Thank you for your consideration. I will be contacting the Agency in a few weeks to discuss the possibility of a meeting. Please do not hesitate to contact me (202-408-7101) if you have any questions.

Sincerely,

Mary Devlin Capizzi

Mary Devlin Capizzi
IPAC Secretariat and Legal Counsel

Enclosure

ITFG/IPAC Collaboration

CMC Specifications Technical Team

Dose Content Uniformity Working Group

Initial Assessment of the ITFG/IPAC Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration

31 July 2000

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I. OVERVIEW

- Between October 1998 and June 1999, the FDA issued the following CMC draft Guidances for Industry: 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation;* and 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation.*

- On 3-4 June 1999, the FDA/AAPS/USP sponsored a Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery. At the Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft CMC Guidances.

- The Inhalation Technology Focus Group (ITFG) supported IPAC's proposal at the June Workshop and agreed to collaborate with IPAC in order to combine scientific expertise and regulatory knowledge and address key CMC issues in the draft Guidance documents. The ITFG/IPAC Collaboration consists of five Technical Teams overseen by a Steering Committee. Over one hundred individuals from more than twenty companies are participating in the ITFG/IPAC Collaboration.

- In October 1999, the FDA created the OINDP Expert Panel (currently the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science) to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft OINDP Guidances. On 26 April 2000, the OINDP Subcommittee held its first meeting, during which the ITFG/IPAC Collaboration reported on its work and made certain commitments to provide the Agency and OINDP Subcommittee with relevant technical reports.

- At the 26 April OINDP Subcommittee meeting, the Dose Content Uniformity (DCU) Working Group of the CMC Specifications Technical Team of the ITFG/IPAC Collaboration reported that, based on the collective experience of its members, it deemed it important to investigate the following question: Can the current state of OINDP technology generally comply with the DCU specifications in the draft FDA CMC Guidances? The DCU Working Group also committed to collect a worldwide database of DCU in OINDP in order to investigate this question.

- The DCU database collected by the ITFG/IPAC Collaboration contains data for 77 products (from 10 companies) with a total of 46016 individual DCU observations. Five products are for nasal delivery and 72 are for oral inhalation.

- Because of the limited number of nasal products available in the database, no valid conclusion can be drawn concerning general characteristics of different product types for nasal delivery.

- The initial assessment of the database supports the hypothesis that orally inhaled products do not in general comply with the DCU specification in the FDA's draft Guidances. The relatively large differences among products and among product types suggest that a single content uniformity specification for all orally inhaled products is not suitable.

- A more detailed analysis will follow employing simulations to address such issues as probability of compliance with complex criteria and which may include studies to compare alternate (statistical) approaches for DCU testing.

II. INTRODUCTION

At the public hearing of the meeting of the Advisory Subcommittee for Orally Inhaled and Nasal Drug Products (OINDP) of the Advisory Committee for Pharmaceutical Science held on 26 April 2000, the ITFG/IPAC Specifications Technical Team put forward the following hypothesis:

> "The current state of OINDP technology may not allow general compliance with the dose content uniformity specifications in the draft FDA CMC Guidances."

Further, at the same meeting, the FDA asked the OINDP Subcommittee the following questions:

- "Should there be a single content uniformity standard for all orally inhaled and nasal drug products (OINDPs)?" and
- "Should the FDA continue development of the proposed statistical approach to evaluating content uniformity?"

To investigate our hypothesis and to provide guidance on the FDA's questions, the Specifications Team committed to collect a worldwide blinded database containing delivered dose content uniformity (DCU) data for OINDP products. Further, the Specifications Team committed to present an initial assessment of the collected DCU data by 31 July 2000. This is the topic of the present report.

This initial assessment is limited to a descriptive analysis of summary characteristics of groups of data. This allows only broad conclusions to be drawn, which nevertheless provides an initial answer to the first question posed by FDA and to the Team's hypothesis. A more detailed analysis will follow in order to maximize the benefits of the database, which is unique in its scope and depth. The detailed analysis will need to employ simulations to address such issues as probability of compliance with criteria on average delivered dose and individual determinations, both for Between Container and for Through Container Life testing. Moreover, the database provides an excellent opportunity to study and compare different tests and sets of criteria for DCU using real data. Thus, although we are not currently in a position to offer any comments on the Agency's second question regarding the development of a statistical approach to evaluating content uniformity, we expect that such considerations may be included in our detailed assessment of the DCU database.

III. DATA COLLECTION

Pharmaceutical companies participating in the IPAC/ITFG Collaboration were asked to submit delivered dose data for as many products as possible. Individual determinations for commercial products and products in late development, obtained at release testing and/or real time stability studies were requested. Data were presented as a percent of delivered dose label claim (LC). To avoid bias, it was recommended that companies submit either:

- all available data for the product, or
- data for a random selection of batches, or
- data for all batches manufactured during a defined time-span.

To ensure blinding of raw data and preserve confidentiality, data for each product were separately submitted in a standardized form to the IPAC Secretariat, which assigned a random code to each file. After checking and necessary clarifications, the coded files were merged into a Master Clean File containing all files that had been finalized by 26 July 2000.

IV. STRUCTURE OF DATA

For each individual DCU determination in the database, the following information was provided by the submitting company: batch number (coded to preserve confidentiality), unit number (*i.e.*, container/can/device number), life-stage (beginning, middle, end, or N/A), and months of storage. Furthermore, the following information describing the product was requested in order to provide an opportunity to study relevant groupings of products:

Table 1. Product information categories (top row) and options for answers.

Product status	Delivery route	Formulation type	Device type	Metering system	# of actuations for minimal clinical dose	# of actuations for one determination
US commercial	Nasal	Dry Powder	CFC	Device metered	1	1
Non-US Commercial	Pulmonary	Solution	HFA	Pre-metered	2	2
Phase IIB/III/NDA		Suspension	Non-pressurized		3	3
			Power assisted		4	4
			Container only		>4	>4
						Same as labeled dose

For each of the categories, submitting companies had the option not to disclose the information (however, this option was very rarely used). Finally, if data for stored samples was submitted, the real time storage condition could be stated.

Original data were provided by 10 companies. The DCU database contains data for 77 products with a total of 46016 individual observations. The number of determinations per product varies from 24 (all from 1 batch) to 3658 (from 18 different batches). About 46% of the results are collected through initial (release) testing, and the remaining 54% are from stability tests. Five products are for nasal delivery, and 72 products are for oral inhalation.

To investigate the Team's hypothesis in an appropriate manner, it was decided to separate from the main assessment those products for which:

- the delivery route is nasal (results for the few nasal products are presented individually);

- the number of actuations in one determination exceeds the number of actuations constituting the minimal clinical dose (since the draft CMC Guidances require that the number of actuations per determination does not exceed the number of actuations per clinical dose); or

- the overall product mean is outside 90-110% LC (since off-target products cannot appropriately represent the general ability to comply with the proposed uniformity requirements).

In total, 17 products were excluded by these requirements, leaving 60 products and 36296 determinations for the main analysis. The excluded products are treated separately.

For each product, the data were summarized by the following characteristics: the number of determinations, the overall mean dose, the overall relative standard deviation (RSD) of delivered dose, and the frequency of determinations outside 75-125% LC (f25) (this interval equals the outer attribute limits of the DCU specification in the draft Guidances).

V. RESULTS AND DISCUSSION

A. Products Excluded from Main Analysis

In total, 17 products did not meet the criteria for being included in the main analysis. Of these 17 products, 12 were orally inhaled products and 5 were nasal products.

1. Orally Inhaled Products

Four products were excluded from the main analysis because the overall product mean was outside 90-110% LC.

Nine products were excluded from the main analysis because the number of actuations per determination exceeded that of the clinical dose (one of which also had an overall product mean outside 90-110% LC). The number of actuations per determination was two or more times higher than the number of actuations per the minimal clinical dose. All 9 products excluded for this reason were suspension pMDIs, two development products formulated with HFA and seven US Commercial products formulated with CFC. A summary of product characteristics is given in Table 2. For the US commercial CFC pMDIs, the RSD ranged between 5.7-11.2% (mean 7.6%, median 6.4%) with f25 varying between 0.0-2.3% (mean 0.7%, median 0.3%). Because the variability of a determination is reduced by increasing the number of actuations, the variability of a determination defined according to the draft Guidances would be higher than indicated by these figures.

Table 2. Summary characteristics for groups of products using more actuations per determination than in clinical dose.

Product status	*Formulation type*	*# of products*	*Total # of determinations*	*Average # of act. per clinical dose*	*Average# of act. per determ.*	*Grand Mean % LC*
Phase IIB-NDA	HFA	2	580	1.0	2.0	96
US Commercial	CFC	7	1901	1.7	3.7	102

Table 2 Continued.

Product status	*Formulation type*	*RSD %*			*f25 %*		
		Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
Phase IIB-NDA	HFA	8.7	*	6.7-10.6	2.9	*	1.7-4.0
US Commercial	CFC	7.6	6.4	5.7-11.2	0.7	0.3	0-2.3

* not meaningful

2. Nasal Products

Table 3 shows product characteristics for the 5 submitted nasal products. All are device-metered suspensions, either in pressurized (CFC and HFA) or non-pressurized formulations. As seen from the table, the RSD varies between 3.6-11.0% with f25 varying between 0.0-2.3%. The number of actuations per determination is greater, lesser or equal to the number of actuations in the clinical dose. Because of the limited number of products available in the database, no valid conclusion can be drawn concerning general characteristics of different product types for nasal delivery.

Table 3. Nasal products (all are device-metered suspensions)

Product status	*Formulation type*	*# of act. per clinical dose*	*# of act. per determ.*	*# of determ.*	*Mean % LC*	*RSD %*	*f25 %*
Phase IIB-NDA	HFA	2	2	2230	99	11.0	2.3
Phase IIB-NDA	HFA	2	2	900	101	6.7	0.1
US Commercial	CFC	2	4	1310	100	10.2	1.5
US Commercial	Non-pressurized	1	2	520	102	3.6	0.0
US Commercial	Non-pressurized	4	2	1200	100	4.8	0.0

B. Main Analysis (Orally Inhaled Products)

The products were grouped according to product status (Table 4) or product type (Table 5). These groups were summarized by taking the mean, median and range of the individual mean product characteristics. This approach (giving each product the same weight in the analysis) was taken to avoid bias from products with a large number of determinations.

Overall, the frequency of DCU determinations outside 75-125% LC varies between 0-14%, with a mean of 2.3% and a median of 1.1% (see Table 4). Results outside the outer attribute limits were reported for the majority (68%) of the products. The relative standard deviation varies between 3.5-18.1% (mean 9.1%, median 8.6%). Table 4 shows that the lowest variability is displayed by US commercial products, which at least partly is due to the fact that these products also had the highest average number of actuations per determination. As noted above, an additional seven US commercial products did not meet the criteria for being included in the main analysis because the number of actuations per determination exceeded the minimal clinical dose. Of the thirteen US Commercial products (6+7), twelve are CFC pMDIs and one is a pre-metered DPI. All of the submitted CFC pMDI data pertain to US Commercial products.

Table 4. Summary characteristics for different groups of product status.

Product status	*# of products*	*Total # of determinations*	*Average # of act. per determination*	*Grand Mean % LC*
US commercial	6	2626	1.8	97
Non-US commercial	16	12259	1.1	98
Phase IIB/III/NDA	36	21171	1.3	101
Not Disclosed	2	240	1.0	100
All	60	36296	1.3	100

Table 4 Continued.

Product status	*RSD %*			*f25 %*		
	Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
US commercial	6.9	6.8	5.8-8.3	0.5	0.4	0-1.4
Non-US commercial	9.6	9.3	5.3-16.7	3.0	1.2	0-14
Phase IIB/III/NDA	9.1	8.7	3.5-18.1	2.3	1.3	0-11
Not Disclosed	11.4	*	11.1-11.6	2.9	*	2.5-3.3
All	9.1	8.6	3.5-18.1	2.3	1.1	0-14

* not meaningful

Table 5. Summary characteristics for different groups of product type.

Product status	*# of products*	*Total # of determinations*	*Average # of act. per determination*	*Grand Mean % LC*
Device metered DPI	19	22985	1.1	100
Pre-metered DPI	17	2020	1.0	100
CFC suspension pMDI	5	2526	2.0	97
HFA suspension pMDI	18	7533	1.5	99
HFA solution pMDI	1	1232	1.0	107
All	60	36296	1.2	100

Table 5 Continued.

Product status	*RSD %*			*f25 %*		
	Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
Device metered DPI	11.0	11.1	6.2-16.7	4.6	3.3	0-14
Pre-metered DPI	6.3	6.0	3.5-8.6	0.3	0.0	0-1.9
CFC suspension pMDI	7.0	7.1	5.8-8.3	0.6	0.7	0-1.4
HFA suspension pMDI	10.2	9.4	8.1-18.1	2.2	1.3	0-7.8
HFA solution pMDI	11.4	*	11.4	6.7	*	11.4
All	9.1	8.6	3.5-18.1	2.3	1.1	0-14

* not meaningful

A comparison of RSD and f25 of different product types presented in Table 5 reveals that different product types have differing characteristic variabilities. Table 5 also demonstrates that device-metered DPIs on average display greater variability than other product types, and pre-metered DPIs on average display lower variability. For pMDIs, the database appears to indicate that an average HFA formulation shows greater variability than an average CFC formulation. There is only one HFA solution pMDI product in the database and therefore no conclusion can be drawn for this product type at this point.

The difference among product types shown in Table 5 and the fact that the RSD and f25 vary over large ranges demonstrate that the DCU characteristics of different products are significantly different, which thus indicates that a single content uniformity specification for all orally inhaled products may not be suitable. The product types that on average appear to show the highest degree of compliance with the draft Guidance specification are CFC suspension pMDIs and pre-metered DPIs.

To illustrate one consequence of having a certain small portion of the DCU results outside 75-125%, we would like to present the following simple example: Assume a product consistently shows 1% of DCU determinations outside the outer limits. The probability of obtaining at least one such result in a test in which 16 determinations are collected (10 determinations in a Between Container test and an additional 6 determinations to complete a Through Container Life test for three of these containers) is $1-0.99^{16} = 0.15$; that is, 15% of such tests would show non-compliance with the outer attribute limits. Given that a typical stability program comprises more than thirty such tests, it is virtually certain that this hypothetical product would fail at some point of its DCU testing program. It is worth noting here that more than half of the orally inhaled products in the current database have DCU results outside 75-125% with a frequency higher than 1%.

The example above suggests a high rate of non-compliance with the DCU specification in the draft Guidances for the majority of the orally inhaled products in the database. From this initial assessment, the database appears to support the Team's hypothesis that orally inhaled products do not in general comply with the DCU specification in the draft CMC Guidances.

VI. CONCLUSION

The initial assessment of the database supports the hypothesis that orally inhaled products do not in general comply with the DCU specification in the FDA's draft Guidances. The relatively large differences among products and among product types suggest that a single content uniformity specification for all orally inhaled products is not suitable.

VII. GLOSSARY

CMC	Chemistry, Manufacturing, and Controls
DCU	Dose Content Uniformity
f25	frequency of DCU determinations outside 75-125% LC
IPAC	International Pharmaceutical Aerosol Consortium, an association of companies that develop and manufacture orally inhaled and nasal products for local and systemic treatment of asthma, chronic obstructive pulmonary disease (COPD), rhinitis, and migraine, as well as new products for non-respiratory disease indications such as diabetes
ITFG	Inhalation Technology Focus Group of the American Association of Pharmaceutical Scientists which is comprised of pharmaceutical scientists who seek to foster and advance the art and science of pharmaceutical aerosol products, aerosol technology and related processes
LC	Label Claim
OINDP	Orally Inhaled and Nasal Drug Products
outer limits	75-125% LC as recommended by the draft Guidances
RSD	Relative Standard Deviation

August 29, 2000

BY OVERNIGHT DELIVERY AND VIA E-MAIL

Nancy Chamberlin
Executive Secretary and Advisory Consultants Staff
Center for Drug Evaluation and Research
Food and Drug Administration
5630 Fishers Lane - Room 1093
Rockville, MD 20857

Re: FDA's draft *Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products: Chemistry, Manufacturing, and Controls Documentation,* dated November 13, 1998; and FDA's draft *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products; Chemistry, Manufacturing, and Controls Documentation,* dated June 2, 1999

Dear Ms. Chamberlin:

On behalf of the ITFG/IPAC Collaboration, I am transmitting herewith the *Initial Assessment of the ITFG/IPAC Particle Size Distribution (PSD) Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration.* This document, prepared by the PSD Working Group of the ITFG/IPAC Collaboration, constitutes part of the work described by the ITFG/IPAC Collaboration in its presentation to the Orally Inhaled and Nasal Drug Products (OINDP) Subcommittee on April 26 of this year. Please post this document on the FDA's website for the OINDP Subcommittee and circulate it to interested persons at the FDA and the members and invited guests of the OINDP Subcommittee. We appreciate the opportunity to provide this report and hope it is of value to the Agency as it develops the relevant Guidances.

The initial assessment is a first step in the analysis of the PSD database compiled by the ITFG/IPAC Collaboration. We would appreciate an opportunity to meet with appropriate representatives from the Agency to discuss the FDA's views on our PSD initial assessment as well as to consider our plans for preparing a more detailed analysis.

Thank you for your consideration. I will be contacting the Agency in a few weeks to discuss the possibility of a meeting to discuss our PSD initial assessment. Please do not hesitate to contact me (202-408-7101) if you have any questions.

Sincerely,

Mary Devlin Capizzi

Mary Devlin Capizzi
IPAC Secretariat and Legal Counsel

Enclosure

ITFG/IPAC Collaboration

CMC Specifications Technical Team

Particle Size Distribution Working Group

Initial Assessment of the ITFG/IPAC Aerodynamic Particle Size Distribution Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration

29 August 2000

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I. OVERVIEW

- Between October 1998 and June 1999, the FDA issued the following CMC draft Guidances for Industry: 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation;* and 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation.* (These draft Guidances are available at http://www.fda.gov/cder/guidance/index.htm).

- On 3-4 June 1999, the FDA/AAPS/USP sponsored a Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery. At the Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft CMC Guidances.

- The Inhalation Technology Focus Group (ITFG) of the AAPS supported IPAC's proposal at the June Workshop and agreed to collaborate with IPAC in order to combine scientific expertise and regulatory knowledge of both organisations and address key CMC issues in the draft Guidance documents. The ITFG/IPAC Collaboration consists of five Technical Teams overseen by a Steering Committee. Over one hundred individuals from more than twenty companies are participating in the ITFG/IPAC Collaboration.

- In October 1999, the FDA created the OINDP Expert Panel (currently the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science) to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft OINDP Guidances. On 26 April 2000, the OINDP Subcommittee held its first meeting, during which the ITFG/IPAC Collaboration reported on its work and made certain commitments to provide the Agency and OINDP Subcommittee with relevant technical reports.

- At the 26 April OINDP Subcommittee meeting, the Particle Size Distribution (PSD) Working Group of the CMC Specifications Technical Team of the ITFG/IPAC Collaboration reported that, based on the collective experience of its members, it deemed it important to examine the relevancy of the mass balance requirement as a product specification versus a system suitability requirement, and to investigate if fewer than 3-4 stage groupings can provide equivalent control. The PSD Working Group also committed to collect a worldwide database of PSD in OINDP in order to consider these issues.

- The PSD database collected by the ITFG/IPAC Collaboration contains data for 35 products (from 7 companies) with a total of 3606 individual observations. One product is for nasal delivery and 34 are for oral inhalation.

- Because there is only one nasal product in the database, no valid conclusion can be drawn concerning this class of drug product.

- The initial assessment of the database indicates that orally inhaled products do not in general comply with the mass balance requirement proposed in the FDA's draft Guidances and that the proposed requirement is not suitable as a drug product specification. Only 4 out of 35 examined products showed no results outside the proposed mass balance limits.

- A more detailed analysis will follow, which will further address such issues as the relevance of the mass balance criterion as either a specification or system suitability criterion and which may include studies to compare different metrics and sets of criteria for characterizing the PSD of OINDP.

II. INTRODUCTION

During the 26 April 2000 meeting of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science, the ITFG/IPAC Specifications Technical Team reported that, with respect to aerodynamic particle size testing in the draft FDA CMC Guidances, it intended to:

- Examine the relevancy of the mass balance requirement as a product specification versus a system suitability requirement; and
- Investigate if fewer than 3 to 4 stage groupings can provide equivalent control.

In order to carry out these investigations, the Specifications Team committed to collect a worldwide, blinded database containing particle size distribution (PSD) data for OINDP. Furthermore, the Specifications Team committed to present the Agency and the Subcommittee with an initial assessment of the collected PSD data. This is the topic of the present report.

This initial assessment contains i) a descriptive analysis of summary characteristics of products grouped by different categories and ii) an investigation of the suitability of the mass balance requirement proposed in the draft CMC Guidances. The initial assessment allows only broad conclusions to be drawn. A more detailed analysis, which is to follow, will further examine the relevancy of the mass balance requirement as a product specification versus system suitability requirement and will also consider if fewer than 3-4 stage groupings can provide adequate control of PSD.

Moreover, the collected PSD database provides a unique opportunity to study and compare different metrics and sets of criteria for characterizing the PSD of OINDP. A subsequent detailed analysis will maximize the benefits of the database, which is unique in its scope and depth. The Specifications Team is continuing to solicit additional data to augment the current database.

III. DATA COLLECTION

Pharmaceutical companies participating in the IPAC/ITFG Collaboration were asked to submit aerodynamic particle size data for individual stages for as many products as possible. Individual determinations for commercial products and products under development (*i.e.*, before Phase IIB through NDA and later), obtained at release testing and/or for real time stability studies were requested. Data were presented as a percent of the label claim (LC). To avoid bias, it was recommended that companies submit either:

- all available data for the product, or
- data for a random selection of batches, or
- data for all batches manufactured during a defined timespan.

To ensure blinding of raw data and to preserve confidentiality, data for each product were separately submitted in a standardized form to the IPAC Secretariat, which assigned a random code to each datafile. After checking and necessary clarifications, the coded files were merged into a Master Clean File containing all files that had been finalized by 9 August 2000.

IV. STRUCTURE OF DATA

For each individual PSD determination in the database, the following information was provided by the submitting company: batch number (coded to preserve confidentiality), unit number (*i.e.*, container/can/device number), life-stage (beginning, middle, end, or N/A), months of storage, apparatus used and particle size ranges for all stages. Furthermore, the following information describing the product was requested in order to provide an opportunity to study relevant groups of products: product status, delivery route, formulation type, device type, metering system and number of actuations per determination. Table 1 lists these categories along with the options for answers. For each of the categories, the companies had the option not to disclose the information; however, this option was very rarely used. Finally, if data for stored samples were submitted, the real time storage conditions could be stated.

Table 1. Product information categories (top row) and options for answers.

Product status	Delivery route	Formulation type	Device type	Metering system	Number of actuations per determination
US commercial	Local pulmonary	Suspension	CFC	Pre-metered	1
Non-US commercial	Local nasal	Solution	HFA	Device metered	2
Phase IIB/III/NDA	Systemic pulmonary	Dry Powder	Non-pressurized		3
Before phase IIB	Systemic nasal		Power assisted		4
			Container only		5
					6
					7
					8
					9
					10
					>10

Seven companies provided original data. The current PSD database contains data for 35 products with a total of 3606 individual observations. The number of determinations per product varies from 9 (all from one batch) to 279 (from five batches). About 49% of the results are collected through initial (release) testing, and the remaining 51% are from

stability tests. One product is for nasal delivery and 34 products are for oral inhalation. The PSD data supplied by the companies were obtained using one of the following apparatus: Andersen cascade impactor, modified Andersen cascade impactor, multistage liquid impinger or IMPAQ (a type of multi-stage cascade impactor).

To examine the mass balance (MB) requirement in an appropriate manner, it was decided to separate from the main assessment those products for which:

- the delivery route is nasal (the single nasal product is presented individually); or

- the MB mean is outside 90-110% LC (since these products cannot appropriately represent the general ability of the product category to comply with the MB requirement proposed in the draft CMC Guidances).

In total, 12 products were excluded because of these considerations, leaving 23 products and 2927 determinations for the main analysis. All of the 23 products included in the main analysis are for local pulmonary delivery. The excluded products were treated separately and the results are presented in Section V.A below.

For each product, the mass balance obtained in each determination was calculated as a sum of the results on all stages and accessories. These individual MB values were then rounded to the nearest integer before the statistical analysis.

For the initial analysis presented here, the data for each product were summarized by the following characteristics: the number of determinations, the mass balance mean, the relative standard deviation (RSD) of the mass balance and the frequency of determinations outside 85-115% LC (f15) (this interval equals the outer limits of the proposed PSD mass balance specification in the draft Guidances).

V. RESULTS AND DISCUSSION

A. Products Excluded from Main Analysis

As stated above, 12 products were excluded from the main analysis. Tables 2a and 2b summarize characteristics of these products. In the case of the single nasal product submitted, this product was eliminated because it was the only product in this class (this product is described in the first row of Table 2a). As a result, we concluded that there was insufficient data to comment on this class of drug products.

The remaining 11 products excluded from the main analysis were separated because their mean mass balance fell outside 90-110% LC. It is obvious without statistical treatment that products in this category will have difficulty meeting the MB requirement of 85-115% LC. In particular, all eight of the power assisted devices demonstrated mass balances on the order of 50% (Table 2b). In this class of drug products, there were no results that met the proposed mass balance requirement. These very low MB values may relate to the interpretation of the draft CMC Guidance. The draft CMC Guidance states that:

> *The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis.*
> (Lines 624-626 of the *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation* draft Guidance); and
>
> *The total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per spray basis.*
> (Lines 759-761 of the *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation* draft Guidance).

The interpretation of this recommendation is problematic because the label claim on a product may not necessarily refer to the amount of drug collected on all the stages and accessories. (As one example, for DPIs that use pre-metered blisters or capsules, the label claim may be based on the amount in the blister or capsule rather than the amount emitted by the device. Since the capsule or blister residual is not quantitated during a particle size determination, obtaining 100% LC mass balance is not possible.) Therefore, it is recommended that the draft Guidances acknowledge the diversity of products and allow the mass balance metric - if it is retained in the Guidances at all - to be defined for each product individually.

Table 2a. Summary characteristics for products excluded from the main analysis.

Product status	*Number of products*	*Formulation*	*Number of actuations per determination*	*Total number of determinations*	*Mean Mass Balance % LC*	*RSD*	*f15**
IIB - NDA	1	HFA pMDI	2	159	100.1	9.9	12.6
IIB - NDA	1	Device-metered DPI	10	83	89.2	10.3	28.9
Non-US Commercial	1	Device-metered DPI	1	192	83.8	9.7	51.0
US Commercial	1	CFC pMDI	>10	96	77.7	4.1	100.0

* frequency of mass balance determinations outside 85-115% LC

Table 2b. Summary characteristics for the group of power-assisted solution drug products excluded from the main analysis

Product status	*Number of products*	*Number of actuations per determination (range)*	*Total number of determinations*	*Mean Mass Balance % LC*	*RSD %*		
					Mean	*Median*	*Range*
before Phase IIB	8	1-10	149	56.5	9.3	8.9	2.5-14.5

B. Main Analysis (Orally Inhaled Products)

The products were grouped according to product status (Table 3), product type (Table 4) or the number of actuations used per determination (Table 5). The summary characteristics of each group are represented by the mean MB and the mean, median and range (for RSD and f15) of the corresponding mean product characteristics. This approach (*i.e.*, giving each product the same weight in the analysis) was taken to avoid bias from products with a large number of determinations.

The results presented in Tables 3, 4, and 5 suggest that there is relatively little difference in the mean MB or the variability of MB (as assessed by RSD) among different groups of products. In particular, the number of actuations per determination does not seem to influence the mean MB or the variability in the range of 1 to >10 actuations per determination (see Table 5).

The mean MB for the 23 products in the main analysis (97.0%, see Table 3), is less than 100% LC. This is probably explained by the nature of a mass balance determination where the analyst is faced with recovering all of the aerosolized dose from a complex device containing a large surface area. This would imply that any acceptance criteria for mass balance should reflect these inherent losses and not be centered on the absolute recovery criterion of 100% LC.

The frequency (f15) of MB determinations outside 85-115% LC varies between 0.0-28.6%, with a mean of 6.6% and a median of 4.8%. Results outside the MB limits proposed in the draft Guidances were reported for the majority (19 out of 23) of the products included in the main analysis. The relative standard deviation varies by product between 3.6-16.7% (mean 7.6%, median 7.1%).

To illustrate a consequence of the MB requirement being applied as a drug product specification, we present the following example: Assume a release test stipulates that 2 units should each be characterized through-life (in the beginning and in the end); that is, 4 determinations are to be made. If the risk to fail the MB requirement (85-115% LC) in an individual determination is 4.8% (equal to the median f15 for products in the main analysis), the risk of failing any arbitrary batch (at least one determination outside 85-115% LC) is $1-(1-0.048)^4 = 0.18$; that is, on average, 18% of batches will fail to comply with the MB requirement. Given that a typical stability program includes a battery of such PSD tests, it is virtually certain that an average product would fail the 85%-115% LC criterion at some point of its PSD testing program.

The actual results from the surveyed products and the example above suggest a high rate of non-compliance with the proposed PSD mass balance specification in the FDA's draft CMC Guidances for the majority of the orally inhaled products. From this initial assessment, the database appears to indicate that the mass balance requirement proposed in the draft CMC Guidances is not suitable as a specification.

We believe that it is not appropriate to use the mass balance requirement in this way (*i.e.*, where it is essentially measuring the emitted dose rather than a characteristic of the size distribution of the batch). For certain products, obtaining adequate information about the particle size distribution may not require achieving an 85-115 % LC mass recovery. We also note that emitted dose is adequately controlled by appropriate specification tests.

Table 3. Summary characteristics for different groups by product status.

Product status	*Number of products*	*Total number of determinations*	*Mean MB* % LC*	*RSD %*			*f15*** %*		
				Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
US commercial	6	866	96.7	5.4	5.2	3.6-8.4	1.8	0.5	0.0-4.9
Non-US commercial	6	622	96.8	7.5	8.0	4.4-10.0	7.2	6.2	0.0-16.8
Phase IIB/III/NDA	10	1404	97.8	8.7	7.8	5.2-16.7	6.9	4.7	0.0-23.8
Not Disclosed	1	35	91.5	11.8	**	**	28.6	**	**
All	23	2927	97.0	7.6	7.1	3.6-16.7	6.6	4.8	0.0-28.6

Table 4. Summary characteristics for different groups by product type.

Product type	*Number of products*	*Total number of determinations*	*Mean MB* % LC*	*RSD %*			*f15*** %*		
				Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
Device metered DPI	13	1706	97.4	8.7	8.1	5.2-16.7	8.1	6.7	0.0-23.8
CFC suspension pMDI	5	854	97.7	5.6	5.3	3.6-8.4	2.1	0.6	0.0-4.9
HFA suspension pMDI	4	166	93.6	7.3	6.5	4.3-11.8	8.4	2.5	0.0-28.6
HFA solution pMDI	1	201	101.4	6.2	**	**	1.5	**	**

Table 5. Summary characteristics for different groups by numbers of actuations per determination.

Number of actuations per determination	*Number of products*	*Total number of determinations*	*Mean MB* % LC*	*RSD %*			*f15*** %*		
				Mean	*Median*	*Range*	*Mean*	*Median*	*Range*
1	5	890	98.9	7.1	6.9	5.8-8.6	4.7	4.3	0.7-12.2
2	2	267	100.9	6.9	6.9	5.3-8.4	2.8	2.8	0.6-4.9
10	5	536	95.9	9.8	10.4	7.1-11.8	15.0	13.6	1.7-28.6
>10	11	1234	95.9	7.0	5.5	3.6-16.7	4.3	1.5	0.0-16.8

* mean of the product MB means
** not meaningful (n=1)
*** frequency of mass balance determinations outside 85-115% LC

VI. CONCLUSION

The initial assessment of the database indicates that orally inhaled products do not in general comply with the proposed mass balance requirement in the draft CMC Guidances (85-115% LC) and that the proposed requirement is not suitable as a drug product specification but could be appropriate as a system suitability test defined on a case by case basis.

VII. GLOSSARY

AAPS	American Association of Pharmaceutical Scientists
CFC	Chloroflourocarbon, a type of propellant used in pMDIs
CMC	Chemistry, Manufacturing, and Controls
DPI	Dry Powder Inhaler
f15	frequency of mass balance determinations outside 85-115% LC
HFA	Hydrofluoroalkane, a type of propellant used in pMDIs
IMPAQ	a brand name for a commercially available multi-stage cascade impactor used for aerodynamic particle sizing
IPAC	International Pharmaceutical Aerosol Consortium, an association of companies that develop and manufacture orally inhaled and nasal products for local and systemic treatment of asthma, chronic obstructive pulmonary disease (COPD), rhinitis, and migraine, as well as new products for non-respiratory disease indications such as diabetes
ITFG	Inhalation Technology Focus Group of the AAPS, comprised of pharmaceutical scientists who seek to foster and advance the art and science of pharmaceutical aerosol products, aerosol technology and related processes
LC	Label Claim
MB	Mass Balance
MDI	Metered Dose Inhaler
OINDP	Orally Inhaled and Nasal Drug Products
outer limits	85-115% LC as recommended by the draft Guidances
pMDI	pressurized Metered Dose Inhaler
PSD	Particle Size Distribution
RSD	Relative Standard Deviation

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August 30, 2000

BY OVERNIGHT DELIVERY AND VIA E-MAIL

Nancy Chamberlin
Executive Secretary and Advisory Consultants Staff
Center for Drug Evaluation and Research
Food and Drug Administration
5630 Fishers Lane – Room 1093
Rockville, MD 20857

Re: FDA's draft *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action,* dated 27 May 1999.

Dear Ms. Chamberlin:

On behalf of the ITFG/IPAC Collaboration, we are transmitting herewith the following two papers: (i) *Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs* and (ii) *Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting.*

These documents, prepared by the BA/BE Technical Team of the ITFG/IPAC Collaboration, constitute the work described by the BA/BE Technical Team in its presentation to the Orally Inhaled and Nasal Drug Products (OINDP) Subcommittee on 26 April of this year. We request that you circulate these documents to interested persons at the FDA and the members and invited guests of the OINDP Subcommittee. In addition, we ask that these documents be posted on the FDA's website for the OINDP Subcommittee. We hope that these two technical papers are of value to the Agency as it continues to develop guidance on BA/BE studies for OINDP.

The BA/BE Technical Team would like to discuss with the Agency the enclosed papers and the conclusions contained therein. The BA/BE Team is also willing to address any subsequent BA/BE questions that the Agency may have. Accordingly, we would appreciate an opportunity to meet with appropriate representatives from the Agency. We will contact the Agency in a few weeks discuss the possibility of a meeting.

We appreciate the opportunity to submit these papers to the Agency and hope that they will assist the Agency and the OINDP Subcommittee in their consideration of BA/BE issues. Please note that the BA/BE Team would be happy to participate in and contribute to any future meetings of the OINDP Subcommittee.

Please do not hesitate to contact us at the above referenced phone numbers or email addresses if you have any questions.

Sincerely,

Mary Devlin Capizzi

Mary Devlin Capizzi
IPAC Secretariat and Legal Counsel

Svetlana Lyapustina

Svetlana Lyapustina, Ph.D.
IPAC Science Advisor

Enclosures
c: Dr. Wallace Adams

ITFG/IPAC Collaboration

BA/BE Technical Team

Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs

30 August 2000

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I. EXECUTIVE SUMMARY

The International Pharmaceutical Aerosol Consortium (IPAC) and the Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists share the FDA's goal of assuring the highest levels of safety, efficacy and quality of orally inhaled and nasal drug products. The ITFG/IPAC Collaboration has identified several areas in the draft Guidance for Industry: *Bioavailability (BA) and Bioequivalence (BE) Studies for Nasal Aerosols and Nasal Sprays for Local Action*[1] where scientific rationale can be questioned and where more scientific discussion and debate are needed.

The ITFG/IPAC Collaboration encourages the Agency to solicit additional scientific discussion on BA/BE studies before issuing further guidance in this area. To resolve the outstanding issues expeditiously, the ITFG/IPAC Collaboration strongly recommends that the Agency pursue existing avenues for scientific collaboration between the Agency and outside interested parties, such as the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), or another AAPS/FDA/USP workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery.

[1] Draft Guidance for Industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* available at http://www.fda.gov/cder/guidance/index.htm (1999).

II. BACKGROUND

- Between October 1998 and June 1999, the FDA issued the following draft Guidances for Industry: 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation;* 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation;* and 3) *Bioavailability (BA) and Bioequivalence (BE) Studies for Nasal Aerosols and Nasal Sprays for Local Action.*
- On 3-4 June 1999, the FDA/AAPS/USP sponsored a Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery. At the Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft Guidances for Orally Inhaled and Nasal Drug Products (OINDP).
- In October 1999,The Inhalation Technology Focus Group (ITFG) supported IPAC's proposal at the June Workshop and agreed to collaborate with IPAC in order to combine scientific expertise and regulatory knowledge and address key issues in the draft OINDP Guidance documents. The ITFG/IPAC Collaboration consists of five Technical Teams overseen by a Steering Committee. Over one hundred individuals from more than twenty companies are participating in the ITFG/IPAC Collaboration. The BA/BE Team is formed to address BA/BE issues of OINDP.
- In October 1999, the FDA created the OINDP Expert Panel (currently the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science) to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft OINDP Guidances. On 26 April 2000, the OINDP Subcommittee held its first meeting, during which the ITFG/IPAC Collaboration reported on its work and made certain commitments to provide the Agency and OINDP Subcommittee with relevant technical reports.
- At the 26 April 2000 OINDP Subcommittee meeting, the BA/BE Technical Team of the ITFG/IPAC Collaboration reported that it has developed position statements on in vitro and in vivo testing in the FDA's draft BA/BE Guidance.
- The BA/BE Team's position statement on in vitro testing is: *In vitro testing is essential for pharmaceutical product equivalence and should be included as part of BA/BE Guidance for all nasal and oral inhalation products, but is not currently sufficient for BE approval without establishing in vivo BE.*
- The BA/BE Team's position statement on in vivo testing is: *For BE approval, BA/BE Guidance documents for nasal and oral inhalation drug products for local action should require use of validated human models for in vivo testing for local and systemic exposure, efficacy and safety.*
- At the 26 April meeting, the BA/BE Team committed to submit to the Agency and the OINDP Subcommittee a technical paper on the Team's in vitro and in vivo position statements. This is the topic of the present report.
- The Team also committed to providing the Agency and the OINDP Subcommittee with its perspectives on the BA/BE questions presented by the Agency during the OINDP Subcommittee meeting. A companion paper addressing these questions is being submitted to the Agency simultaneously with this technical report.

III. INTRODUCTION

The BA/BE Technical Team of the ITFG/IPAC Collaboration has focused on the in vitro and in vivo tests in the Agency's draft *Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (draft BA/BE Guidance). Since January 2000, the BA/BE Technical Team has discussed these issues in depth. The Team has agreed on several working assumptions and has identified two main position statements, one for in vitro tests and the other for in vivo tests in the draft BA/BE Guidance. During the past several months, Team members have submitted and evaluated data and scientific articles related to these position statements. The conclusions in this paper are based upon the Team's working assumptions and currently available information.

This paper is closely related to the paper which is being co-submitted by the BA/BE Team to respond to the BA/BE questions presented by the Agency at the OINDP Subcommittee meeting on 26 April. The paper presented here is more general in scope and has a broader perspective than the Team's paper on the Agency's BA/BE questions. There are some significant areas of overlap between the Team's two papers and therefore we request that the Agency and OINDP Subcommittee consult both papers for a complete perspective of the Team's consensus views on BA/BE issues.

The Team has prepared this paper on in vitro and in vivo tests in the draft BA/BE Guidance in order to:

- highlight areas where there are not enough data at present to draw conclusions; and
- review available technical documentation related to BA/BE issues addressed by the Team and offer the Team's conclusions based on that documentation.

The conclusions of this paper are applicable to the draft BA/BE Guidance for Nasal Aerosols and Nasal Sprays for Local Action as well as the Agency's forthcoming draft BA/BE Guidance for orally inhaled drug products. It is recognized that this paper contains relatively few examples relating to nasal issues because of the lack of pertinent nasal data available. Although most of the examples are for pulmonary locally acting drugs, these data may have general applicability to nasal drugs and will be directly relevant for the Agency's future guidance on orally inhaled drug products.

IV. ASSUMPTIONS AND OTHER CONSIDERATIONS

1. Assumptions of BA/BE Technical Team

In preparing this paper, the BA/BE Technical Team has agreed on the following working assumptions:

- Our specific BA/BE recommendations apply to locally acting drugs per the current draft BA/BE Guidance for nasal aerosols and sprays, and should apply, as appropriate, to orally inhaled drug products in the anticipated forthcoming BA/BE Guidance for orally inhaled drugs;
- Our conclusions apply to both orally inhaled and nasal drug products, but these dosage forms should be treated in separate Guidances;
- Scientific and clinical bases for developing BA/BE Guidance are evolving; and
- Our BA/BE working propositions reflect only the current state of knowledge.

2. Definition of Bioequivalence (BE)

As noted in the draft BA/BE Guidance, BA and BE may be established in vivo by measuring both local delivery and systemic absorption/exposure. The draft Guidance equates local delivery with efficacy studies and systemic absorption/exposure with pharmacokinetic (PK) or pharmacodynamic (PD) studies. The BA/BE Team has discussed situations where use of in vitro data plus systemic PK/PD studies may be sufficient to establish BE. This discussion can be found in the BA/BE Team's companion paper which has been submitted to the Agency with this paper.

3. Factors Relating In Vitro Tests to Deposition and to Biological Effect

The biological effect of an inhaled drug is dependent on several factors. First is the mass of particles in the inhaled air stream (emitted dose). Particle size distribution, breathing pattern, and the specific nature of the aerosol delivery from the device are the prime determinants of the deposition pattern in the body. Other deposition factors include the geometry of the airways that can be influenced by disease state. The drug may act locally in the region of deposition, or at a remote site following absorption of the drug into the blood stream and systemic delivery. Thus, there are many factors that can influence biological effect other than the particle size

distribution and emitted dose of the inhaled drug, as has been noted in several reviews (Schlesinger, 1988; Gonda, 1990; Brain and Blanchard, 1993).

The use of in vitro tests of particle size distribution and emitted dose as surrogates for deposition or biological effect must be approached with caution as has been noted previously by individuals and groups assessing this issue. There have been at least two workshops that have examined this question in some detail (Clark, 1998; Snell and Ganderton, 1999). The consensus from both meetings was that in vitro/in vivo comparisons are being developed and in vitro methods are improving to enhance their in vivo applicability, but that as yet it is not possible to rely solely on in vitro data as a predictor of clinical use by patients. The proceedings from these workshops provide in depth considerations of various aspects of this general question and are excellent sources for more detailed discussions.

V. TEAM'S POSITION STATEMENTS

The Team's position statements on in vitro and in vivo tests in the draft BA/BE Guidance are as follows:

1. In Vitro Tests:

In vitro testing is essential for pharmaceutical product equivalence and should be included as part of BA/BE Guidance for all nasal and oral inhalation products, but is not currently sufficient for BE approval without establishing in vivo BE.

2. In Vivo Tests:

For BE approval, BA/BE Guidance documents for nasal and oral inhalation drug products for local action should require use of validated human models for in vivo testing for local and systemic exposure, efficacy and safety.[2]

[2] As addressed in more detail in the BA/BE Team's paper responding to the FDA's BA/BE questions, it is appropriate that sponsors be given the opportunity to present their case for an abbreviated clinical program. If a predictive in vitro/in vivo correlation can be documented from the literature or from new well-documented data, the sponsor should have the opportunity to request waiving all clinical studies.

VI. IN VITRO TESTS IN DRAFT BA/BE GUIDANCE

1. Overview of In Vitro Tests in Draft BA/BE Guidance

The draft BA/BE Guidance utilizes a large battery of in vitro tests in order to evaluate drug product quality of nasal and inhaled dosage forms. In particular, the following tests have been identified in the draft BA/BE Guidance as part of BA and BE determination:

1. Dose or Spray Content Uniformity
2. Droplet and Particle Size Distribution
3. Spray Pattern
4. Plume Geometry
5. Priming and Repriming
6. Tail Off Profile

Spray content uniformity, particle size distribution, spray pattern and priming (if part of product labeling) are considered in vitro determinants of BE utilizing the confidence interval approach. Plume geometry, tail off profile, and particle size characterization through light microscopy may be evaluated as supportive characterization of BE. The draft BA/BE Guidance stresses the importance of conducting in vitro testing in a randomized, blinded fashion in order to eliminate potential analyst bias.

In the following sections, we highlight the issues which have been raised surrounding the use of these tests for the investigation of BE alone or in combination with an in vivo assessment.

2. BA/BE Team's Analysis

2A. In vitro tests described in the draft BA/BE Guidance are not necessarily more relevant or discriminating than clinical studies for BE assessment

The establishment of BA and BE in nasal products for local action requires reliance on clinical endpoint studies. The draft BA/BE Guidance acknowledges that studies of this nature are frequently incapable of showing a dose-response relationship and may not be consistently reproducible. However, in vitro tests for demonstration of bioequivalence also have limitations.

Of the tests utilized for in vitro assessment of nasal and inhalation drug products, droplet and particle size data have received the most attention in the literature. According to the draft BA/BE Guidance, droplet and particle size distribution can be evaluated through several methods, including optical methods (laser diffraction, light scattering, time-of-flight), inertial impactor methods (cascade impactor, multistage liquid impinger), and light microscopy.

Laser diffraction is the suggested method for determination of droplet size distribution. It is especially useful for nasal sprays, because it has enough size range to cover large nasal droplets produced by nasal sprays (Cheng *et al.*, 2000). In general, the method is fast, has good resolution, a broad particle size range, and can be used for measurements of pMDIs, DPIs, and liquid atomizers such as nebulizer systems. The great disadvantage of laser diffraction methods is that they cannot differentiate components of the formulation. In the case of pMDI systems, other disadvantages include sampling errors due to evaporation, overestimation of size distribution due to presence of propellant s, and dilution requirements (Dolovich, 1991; Clark *et al.*, 1998).

Another optical method currently receiving attention is the time-of-flight aerodynamic particle size analyzer. Similar to laser diffraction techniques, this method cannot discriminate between drug and non-drug particles. This method has been investigated for use with pMDIs, DPIs and nebulizers. The present state of the art suggests that this particle sizing method is effective for formulation development and screening, but cannot replace inertial particle size methods such as those described in pharmacopoeial compendia (Mitchell *et al.*, 1999).

Inertial particle size techniques, such as cascade impactors and multistage liquid impingers have a distinct advantage since the methods are capable of distinguishing drug particles, normally through an assay technique. However, the limitations of this method have been well documented. Size distributions among cascade impactors can vary significantly, and thus any comparisons performed in order to establish BA or BE must be evaluated with the same equipment (Stein and Olson, 1997; Stein 1999). In addition, there is concern regarding the use of this equipment for evaluation of nasal products, given that particle sizing stages have been optimized for oral inhalation products, and not for nasal delivery, where MMAD exceed 10 μm (Harrison, 2000).

The spray pattern/plume geometry including plume angle and speed of the plume are also important factors on the distribution of deposited droplets in the nasal airway, and may therefore influence the bioequivalence of nasal drugs (Cheng *et al.*, 2000). High speed photography/video is used to determine the plume geometry/spray pattern. Therefore, we suggest that light microscopy be strictly used as a supportive method for drug and aggregate particle size and morphology evaluation, because of its limitations.

We also believe that in vitro tests are important for the establishment of BA and BE, particularly dose content uniformity and particle size analysis. However, the predictive limitations of the in vitro tests at the present time support the need for in vivo studies.

2B. The assumption that in vitro studies alone are sufficient for BE of solutions is unfounded. The draft BA/BE Guidance should not distinguish between nasal suspensions and solutions for in vivo BE

According to the draft BA/BE Guidance, in vitro tests are sufficient to support approval of solution nasal products. As documented in this paper, in vitro tests for use as BE metrics have limitations. Based on the lack of information on the established relationship between in vitro/in vivo data for OINDP, it is the consensus of the BA/BE Technical Team that in vivo BE determinations should be required. As more data becomes available, removal of in vivo BE testing for solutions could be considered for certain drug classes.

2C. Based on the available literature, current in vitro tests may predict lung deposition, but the utility of those tests to demonstrate clinical equivalence of inhaled drug products has not been shown

The clinical relevance of in vitro data to the in vivo environment has been studied for a variety of products, including inhalation dosage forms. In particular, in vivo lung deposition has been demonstrated to be linked to in vitro estimates of fine particle dose in well controlled studies for cromolyn sodium (Laube *et al.*, 1998). However, such correlations may not hold true for all cases and classes of drug substances used in inhalation and nasal dosage forms. In addition, the ability of in vitro studies to predict clinical effectiveness in general has not been demonstrated. This is an evolving area with considerable promise, but there is yet no validated approach of wide-ranging applicability.

A review of the literature indicates that in certain instances, in vitro results have failed or inaccurately predicted the in vivo results, which would have resulted in a false conclusion regarding BE if in vivo studies had not been conducted. Failure to predict in vivo outcome has been demonstrated in the following two studies. In a study by Borgström *et al.* (2000), the in vitro and in vivo performance (lung deposition) of terbutaline via a pMDI and DPI Turbohaler was evaluated. The variability in lung deposition could not be attributed solely to in vitro variability, which is linked mainly to variability in dose leaving the metering chamber/dosing disk. The interaction of patient geometry (anatomy) and the actual patient handling of the device had a significant influence on the overall variability, which could not be mimicked in the in vitro environment. In another study, two nasal aerosols with different in vitro properties were generated. Although in vitro testing concluded significant differences among the two aerosols, this did not translate into any differences in the in vivo deposition pattern in the nose (Suman *et al.*, 1999). Similar nasal deposition patterns with differing particle sizes was also observed by Hughes *et al.* (1993). The lack of difference in deposition pattern could be a result of poor power of discrimination in the in vivo test and emphasizes the difficulty of measuring nasal deposition patterns in vivo.

Inaccurate predictions of in vivo deposition have also been demonstrated in several studies. A comparison of 11 scintigraphic studies and fine particle fraction measurements conducted on MDIs, DPIs and Soft Mist Inhalers found that in vitro assessment provided an overestimation of actual lung deposition (Newman, 1998) when the standard cut-off diameter of 4.7 micrometers was used. However, Newman (1998) showed that there was a much improved correlation of lung deposition with particles less than 3.3 micrometers. However, it should be noted that this correlation is in all probability descriptive, not predictive; different correlations may be obtained if there are variations in the method used to assess deposition. Another study conducted by Olsson *et al.* (1996) demonstrated improvement in correlation between lung deposition and fine particle fraction through modification of the inlet port on the impinger to mimic the oropharynx. Other recommendations to improve correlations between in vitro measurements and in vivo deposition include use of a multistage apparatus in the range of 0.5 – 5.0 μm. and evaluation on a range of flow rates to mimic the in vivo conditions (Snell and Ganderton, 1999). A recent study on the AERx inhalation system indicated good correlation between the in vitro measurement and in vivo deposition pattern when similar flow rates were utilized (Farr *et al.*, 2000).

The current literature suggests that we can use the available knowledge on the relationship between in vitro and in vivo outcome to run in vitro studies during biopharmaceutical development, but we cannot at the present time use in vitro methods alone to claim in vivo/clinical effect equivalence as a basis for regulatory approval.

VII. IN VIVO TESTS IN DRAFT BA/BE GUIDANCE

1. Overview of In Vivo Tests in Draft BA/BE Guidance

The BE tests[3] recommended by the BA/BE Team for all nasal and orally inhaled drugs fall into the following scheme:

- Clinical efficacy study to document equivalent drug delivery to the local site of action; and
- Systemic exposure study (PK).

The clinical efficacy study is used to assess local delivery of drug and efficacy, whereas the systemic exposures are intended to provide a marker that can be related to safety. Some of the challenges involved in conducting meaningful in vivo studies are that some endpoints are easier to measure than others for particular classes of drugs. This means that it is frequently difficult to assess both local and systemic criteria adequately for all drugs.

For instance, for nasal drugs, it is difficult to have clinical responses that can differentiate two products. However, it may be more difficult to measure systemic exposure of the nasal products considering the low doses administered. For orally inhaled bronchodilators, good methods of quantifying bronchodilator response have been identified (Adams, 1995; Stewart *et al.*, 1999). It is, however, relatively difficult to ascertain a dose-response relation related to efficacy for orally inhaled corticosteroids. These difficulties in adequately assessing BE have been cited frequently (Adams *et al.*, 1994, 1995, 1998; Wong and Hargreave, 1993, Casale *et al.*, 1999; Harrison, 2000). These complexities and differences between exposure routes, classes of drugs, and specific drugs, argue for more flexible approaches. Although the BA/BE Team agrees that the above in vivo BE program should be recommended in the draft BA/BE Guidance, the Team also recommends that the BA/BE Guidance urge sponsors to discuss their in vivo BE program for a specific drug with the Agency.

The following specific issues identified by the BA/BE Technical Team emphasize that both clinical efficacy and systemic exposure (as an indicator of adverse effects) need to be evaluated to provide an adequate assessment of clinical BE.

2. BA/BE Team's Analysis

2A. Systemic PK/PD estimates systemic exposure (*i.e.*, safety) but does not estimate local delivery (*i.e.*, efficacy and local tolerance).

Blood levels of a particular drug obviously reflect the amount of drug absorbed systemically. However, for respiratory tract drugs, absorption can take place from the site of absorption, across tissue and into blood, and also from drug that is translocated by mucociliary clearance from nasal or bronchial airway epithelium, swallowed and then absorbed from the

[3] In this paper, BE is assumed to be BE of clinical efficacy and safety.

gut. Further, there can be differential rates of absorption from various sites in the lung. Many data sets show a higher degree of absorption from the alveolar or pulmonary region than from upper airways (Oberdorster, 1986) although this is compound dependent and is more evident for larger than smaller molecules. Available data support the view that local topical delivery of corticosteroids is responsible for their clinical efficacy both with nasal delivery (Howland, 1996a, 1996b; Lindqvist *et al.*, 1989) and for orally inhaled delivery (Toogood *et al.*, 1990; Lawrence *et al.*, 1997). As a corollary, because the same systemic blood levels can be achieved by different deposition patterns, systemic exposure does not necessarily correlate with efficacy. Thus, we concur with the Agency's position as stated in the draft Guidance.

2B. Efficacy assessments alone cannot establish in vivo BE since they will not assure comparable safety (systemic exposure)

Local delivery BE studies are important to assure equivalent efficacy and local tolerance at the site of action, but the study design does not assure systemic safety, which is a major concern of a new product. Literature data clearly indicates that systemic absorption (as measured by PK) may not correlate with local delivery. Studies comparing oral administration with either nasal or oral inhalation administration for fluticasone propionate and budesonide (see references in the previous section) have shown no correlation between PK and clinical efficacy. Until a linkage is established for a given drug or drug class, caution is advised against any modification of the proposed in vivo BE program that includes both local delivery and systemic absorption/exposure. Thus, we concur with the Agency's position as stated in the draft Guidance.

2C. Lung deposition studies are a promising new technique, but currently cannot replace the local delivery requirement

Local delivery estimated as total material deposited in the lung is not likely to be sufficiently discriminating to be predictive of BE. Two examples are examined to illustrate this point. In a study by Leach (1998), HFA and CFC formulations of beclomethasone dipropionate were compared. Although the emitted doses were the same, the fine particle dose (percent of particle mass < 4.7 micrometers) was higher for the HFA formulation compared to the CFC formulation (56% of emitted dose vs 33%,respectively). Deposition was dramatically different, with the HFA formulation (1.1 μm MMAD) resulting in 56% lung deposition vs 6% for the CFC formulation (3.9 μm MMAD). Clinical efficacy studies showed that the HFA beclomethasone dipropionate formulations did not scale directly with lung deposition, but required approximately half the emitted dose of the CFC formulations. In a non-clinical example, Ruffin *et al.* (1978) compared bronchoconstrictive effects of histamine when inhaled in different modes. Equal lung doses of histamine were given in one mode with a central deposition pattern and in the other mode with a peripheral deposition pattern. Although the total lung doses were equal, the bronchoconstricting effect of histamine was much greater for the central deposition pattern.

The Leach and Ruffin papers point out that regional deposition pattern within the lung is very important for eliciting a biological response, which can differ even if the total lung dose is the same. For instance, bronchodilator response to beta-2 agonists appears to be predominantly related to receptor mediated action on bronchial airway smooth muscle (Barnes, 1995; Nishikawa *et al.*, 1996). Therefore if two formulations have the same total lung dose but

differing bronchial airway doses, biological response is likely to differ. Other drugs with different receptor distributions in the lung and other modes of action will have to be considered on an individual compound basis. If this is the case, then knowing total lung dose will not be sufficient to determine biological response for all pharmacologic agents.

A limitation of the most common lung deposition technique is that the product must be altered by the sponsor to allow for the addition of a radiolabeled tag. In order for the radiolabeled material to serve as a BE standard, data must be provided to show that product properties are essentially unchanged and remain within specifications. Another limitation of the radiolabeled lung deposition technique is that at present, there is no standardized approach to such a study.

2D. Reduction of testing requirements with validated models

In vitro data, regional deposition data, PK/PD studies, and clinical efficacy studies are all likely needed to characterize adequately the relationships going from inhaler and particle characteristics to relate to ultimate clinical effects in patients when a new inhaled drug is developed (Borgström, 1999; Gonda, 1990). (The data derived above for the new HFA formulation of beclomethasone dipropionate is a good example). With sufficient data it should be possible to define the variations around the individual components that results in clinically similar efficacy. Various linkages among the data sets can be envisaged.

If it is possible to determine that a certain range of regional deposition values or PK parameters or in vitro test results correlates with in clinical efficacy within acceptable limits, then future studies might need only to measure regional deposition or PK or in vitro testing within these ranges. Further, if these features could be reliably linked with mathematical models that predict a range of deposition behavior or PK performance or in vitro test results for given input parameters it would be possible to reduce or eliminate reliance on carrying out extensive clinical trials. Until the state of the art improves such that there is more power among the tests relating in-vitro tests to ultimately predict clinical effects, it appears a cautious approach is warranted (Wong and Hargreave, 1993). It is impossible at this time to completely describe a validated model because it will depend on the available data for the particular inhaled drug being developed, and so it is recommended that an approach for each circumstance be negotiated between the sponsor and regulatory agencies.

VIII. CONCLUSION

The ITFG and IPAC share the FDA's goal of assuring the highest levels of safety, efficacy and quality of orally inhaled and nasal drug products and making these products available to patients in the most expeditious manner. We recognize and appreciate the considerable efforts put forth by the Agency in developing guidance on product quality BA and BE studies for OINDP. The ITFG/IPAC Collaboration also commends the Agency for addressing key issues in BA and BE studies at the 26 April OINDP Subcommittee meeting. We are grateful for the opportunity to share with the Agency and the OINDP Subcommittee our perspectives on in vivo and in vitro studies in the draft BA/BE Guidance.

Our comments in this paper are intended to highlight areas in the draft BA/BE Guidance where the scientific rationale can be questioned and where more scientific discussion and debate are needed. The Agency's comments to the OINDP Subcommittee on 26 April underscore the Agency's concerns with some of the positions in the draft BA/BE Guidance. We encourage the Agency to solicit further scientific discussion on these positions before issuing further guidance. In addition, the members of the ITFG/IPAC Collaboration strongly recommend that the Agency continue to utilize existing avenues for scientific collaboration, such as the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), or another AAPS/FDA/USP workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery to gather all interested parties for a data-driven scientific review of key BA/BE issues.

IX. REFERENCES

W. P. Adams. Albuterol MDI In Vivo bioequivalence: FDA's office of generic drugs dose-response studies. *Drug Information Journal*, 29:935-940 (1995).

W. P. Adams. Albuterol MDI in vivo bioequivalence: FDA's Office of Generic Drugs' dose-response studies. *Drug Information Journal* 29: 935-94 (1995).

W. P. Adams, G. Poochikian, A. S. Taylor, R. M. Patel, G. P. Burke, R. L. Williams. Regulatory aspects of modifications to innovator bronchodilator metered dose inhalers and development of generic substitutes. *J. Aerosol. Med.* 7: 119-134 (1994).

L. Adjei, J. Garren. Pulmonary delivery of peptide drugs: Effect of particle size on bioavailability of leuprolide acetate in healthy male volunteers. *Pharm. Res.*, 7, 565-569 (1990).

P. J. Barnes. Beta-adrenergic receptors and their regulation. *Am. J. Resp. Crit. Care Med.* 152: 838-860 (1995).

J. D. Brain and J. D. Blanchard. Mechanisms of particle deposition and clearance. In "Aerosols in Medicine," F. Moren, M. B. Dolovich, M. T. Newhouse, and S. P. Newman, eds., Elsevier, Amsterdam, 117-156 (1993).

L Borgström *et al.* Variability in lung deposition of inhaled drug, within and between athmatic patients, with a pMDI and a dry powder inhaler, Turbuhaler. *Int J Pharm* 193: 227-230 (2000).

L. Borgström. Pharmacokinetics of inhaled hydrofluoroalkane formulations. *J. Allergy.Clin. Immunol.*, 104:S246-S249 (1999).

T. B. Casale, S. Azzam, R. E. Miller, J. Oren and the SAR Study Group. Demonstration of therapeutic equivalence of generic and innovator beclomethasone in seasonal allergic rhinitis. *Annals of Allergy, Asthma & Immunology*, Volume 82, 435-441 (1999).

Y. S. Cheng, T. D. Holmes, J. Gao and R. A. Guilmette, S. Li, Y. Surakitbanharn, and C. Rowlings. Characterization of nasal spray pumps and deposition pattern in human nasal airways. *J. Aerosol Med.* (in press, 2000).

A. R. Clark, I. Gonda and M. T. Newhouse. Introduction to Workshop on the topic of "Towards Meaningful Laboratory Results for Evaluation of Pharmaceutical Aerosols" in January of 1997. The proceeding of that workshop were published in the *Journal of Aerosol Medicine* Volume 11, Supplement 1, S-1 to S-153 (1998).

M. Dolovich. Measurement of particle size characteristics of metered dose inhaler (MDI) aerosols. *J. Aerosol Med.* 4: 251-263 (1991).

S. Farr, S. Warren, P. Lloyd, J. Okikawa, J. Schuster, A. Rowe, R. Rbsamen and F. Taylor. Comparison of in vitro and in vivo efficiencies of a novel unit-dose liquid aerosol generator and a pressurized metered dose inhaler. *Int. J. Pharm.* 198: 63-70 (2000).

I. Gonda. Aerosols for delivery of therapeutic and diagnostic agents to the respiratory tract, *Crit. Rev. in Therap. Drug Carrier Sys.*, 6, 273 (1990).

L. Harrison. Commentary on the FDA guidance for bioequivalence studies for nasal aerosols and nasal sprays for local action: an industry view. *J. Clin. Pharmacol.* 7: 701-707 (2000).

W. C. Howland III, F. C. Hampel, Jr., B. G. Martin, P. H. Ratner, J. H. van Bavel and E. A. Field. The Efficacy of Fluticasone Propionate Aqueous Nasal Spray for Allergic Rhinitis and Its relationship to Topical Effects. *Clin. Therapeutics* 18 (6) 1106-1117 (1996)

W. C. Howland III. Fluticasone propionate: topical or systemic effects? *Clin. Exp. Allergy* 26 (supplement 3): 18-22 (1996).

B. L. Hughes, D. L. Allen, M. A. Dorato and R. K. Wolff. Effect of delivery devices on nasal deposition and mucociliary clearance in Rhesus monkeys. *Aerosol Science and Technology;* 18:241-249 (1993).

B. L. Laube, A. Georgopoulos and G. K. I. Adams. Preliminary study of the efficacy of insulin aerosol delivered by oral inhalation in diabetic patients. *J. Amer. Med. Assoc.* 269, 2106-2109 (1993).

M. Lawrence, J. Wolfe, D. R. Webb, P. Chervinsky, D. Kellerman, J. P Schaumberg and T. Shah. Efficacy of inhaled fluticasone propionate in asthma results from topical and not from systemic activity. *Am J Respir Crit Care Med* 156:744-751 (1997).

C. L. Leach. Relevance of radiolabeled steroid inhalation studies to clinical outcomes, *J. Aerosol Med.* 11, Supplement 1, s-29 to s-34 (1998).

N. Lindqvist, M. Andersson, M. Bende, S. Löth, and U. Pipkorn. The clinical efficacy of budesonide in hay fever treatment is dependent on topical nasal application. *Clin Exp Allergy* 19:71-6 (1989).

J. P. Mitchell and M. W. Nagel. Time-of-flight aerodynamic particle size analyzers: their use and limitations for the evaluation of medical aerosols. *J. Aerosol Med.* 12: 217-240 (1999).

S. P. Newman. How well do in vitro particle size measurements predict drug delivery in vivo. *J. Aerosol Med.* 11: S97-S104 (1998).

M. Nishikawa, J. C. Mak and P. J. Barnes. Effect of short- and long-acting beta 2-adrenoceptor agonists on pulmonary beta2-adrenoceptor expression in human lung. *Eur. J. Pharmacol.* 318(1):123-9 (1996).

G. Oberdorster, M. Utell, P. E. Morrow, R. W. Hyde and D. A. Weber. Bronchial and alveolar deposition of inhaled 99mTc-DTPA. *Am. Rev. Resp. Dis.* 134: 944-950 (1986).

B. Olsson, L. Borgstrom, L. Asking and E. Bondesson. Effect of inlet throat on the correlation between measured fine particle dose and lung deposition. In *Respiratory Drug Delivery*, R. Dalby, P. Byron, S. Farr (eds.), Interpharm Press, Buffalo Grove, IL, 273-281 (1996).

R. E. Ruffin, M. B. Dolovich, R. K. Wolff and M. T. Newhouse. "The effects of preferential deposition of histamine in the human airway," *Am Rev. Resp. Dis.* 117, 485-492 (1978).

R. B. Schlesinger. Deposition and clearance of inhaled particles, in *Concepts in Inhalation Toxicology*, ed. R. O. McClellan and R. F. Henderson (New York: Hemisphere), 163-192 (1989).

N. J. C. Snell and D. Ganderton. Assessing lung deposition of inhaled medications: consensus statement from a workshop of the British Association for Lung Research. *Resp. Med.* 93:123-133 (1999).

S. W. Stein and B. A. Olson. Variability in size distribution measurements obtained using multiple Andersen mark II cascade impactors. *Pharm. Res.* 14: 1718-1725 (1997).

S. W. Stein. Size distribution measurements of metered dose inhalers using Anderson mark II cascade impactors. *Int. J. Pharm.* 186: 43-52 (1999).

B. A. Stewart, R. C. Ahrens, S. Carrier, M. Frosolono, C. Lux, S. H. Han and G. Milavetz. Demonstration of in vivo bioequivalence of a generic albuterol metered-dose inhaler to Ventolin. *Chest*, 117, 714 (1999).

J. D. Suman, B. L. Laube, T. Lin, G. Brouet, R. L. Dalby. In vitro performance measurements of aqueous nasal spray pumps may not predict in vivo deposition pattern. *AAPS PharmSci* 1(4 Suppl):S272 (1999).

J. H. Toogood, C. W. Frankish, B. H. Jennings, J. C. Baskerville, O. Borgå, N. M. Lefcoe, and S. Å. Johansson. A study of the mechanism of the antiasthmatic action of inhaled budesonide. *J. Allergy Clin. Immunol.* 85:872-80 (1990).

B. J. Wong and F. E. Hargreave. Bioequivalence of metered-dose inhaled medications. *J. Allergy Clin. Immunol.* 92:373-9 (1993).

OVERVIEW OF ITFG/IPAC COLLABORATION

Presented by: Harris Cummings, PhD

26 April 2000
Rockville, MD

ITFG

The Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists is comprised of pharmaceutical scientists who seek to foster and advance the art and science of pharmaceutical aerosol products, aerosol technology and related processes

IPAC

The International Pharmaceutical Aerosol Consortium (IPAC) is an association of companies that develop and manufacture orally inhaled and nasal products for local and systemic treatment of asthma, chronic obstructive pulmonary disease (COPD), rhinitis, and migraine, as well as new products for non-respiratory disease indications such as diabetes

DRAFT FDA GUIDANCES FOR OINDP

Draft Guidances for Industry:

1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*;

2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*; and

3) *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*

PERSPECTIVE OF ITFG and IPAC

ITFG and IPAC:

- share FDA's goal of assuring the highest levels of safety, efficacy and quality of OINDP and making these products available to patients expeditiously

- recognize the value of having OINDP guidance documents to facilitate the development and approval of new medications, but believe that differing views surround CMC and BA/BE issues

- believe that these differences need to be resolved through the process of a science-based dialogue so that the OINDP Guidances can bring maximum value to regulators and industry, and most of all, to patients and physicians

BACKGROUND ON THE COLLABORATION

June 1999: AAPS/FDA/USP Workshop on OINDP Regulatory Issues

- IPAC presents a Statement proposing a consensus building process
- The ITFG endorses IPAC's Statement
- The Agency agrees to consider IPAC's proposal further

September 1999: ITFG and IPAC agree to undertake a data-driven collaborative effort

The objectives of the Collaboration are to:

- utilize the combined expertise and experience of scientists from IPAC Member Companies and AAPS Inhalation Technology Focus Group
- expand the knowledge base of the relevant science of OINDP
- facilitate common Understanding on CMC and BA/BE issues in order to provide the Agency and the Subcommittee with timely technical reports and recommendations for consideration during the Subcommittee's deliberations

FRAMEWORK OF THE COLLABORATION

The ITFG/IPAC Collaboration is overseen by the ITFG/IPAC Steering Committee

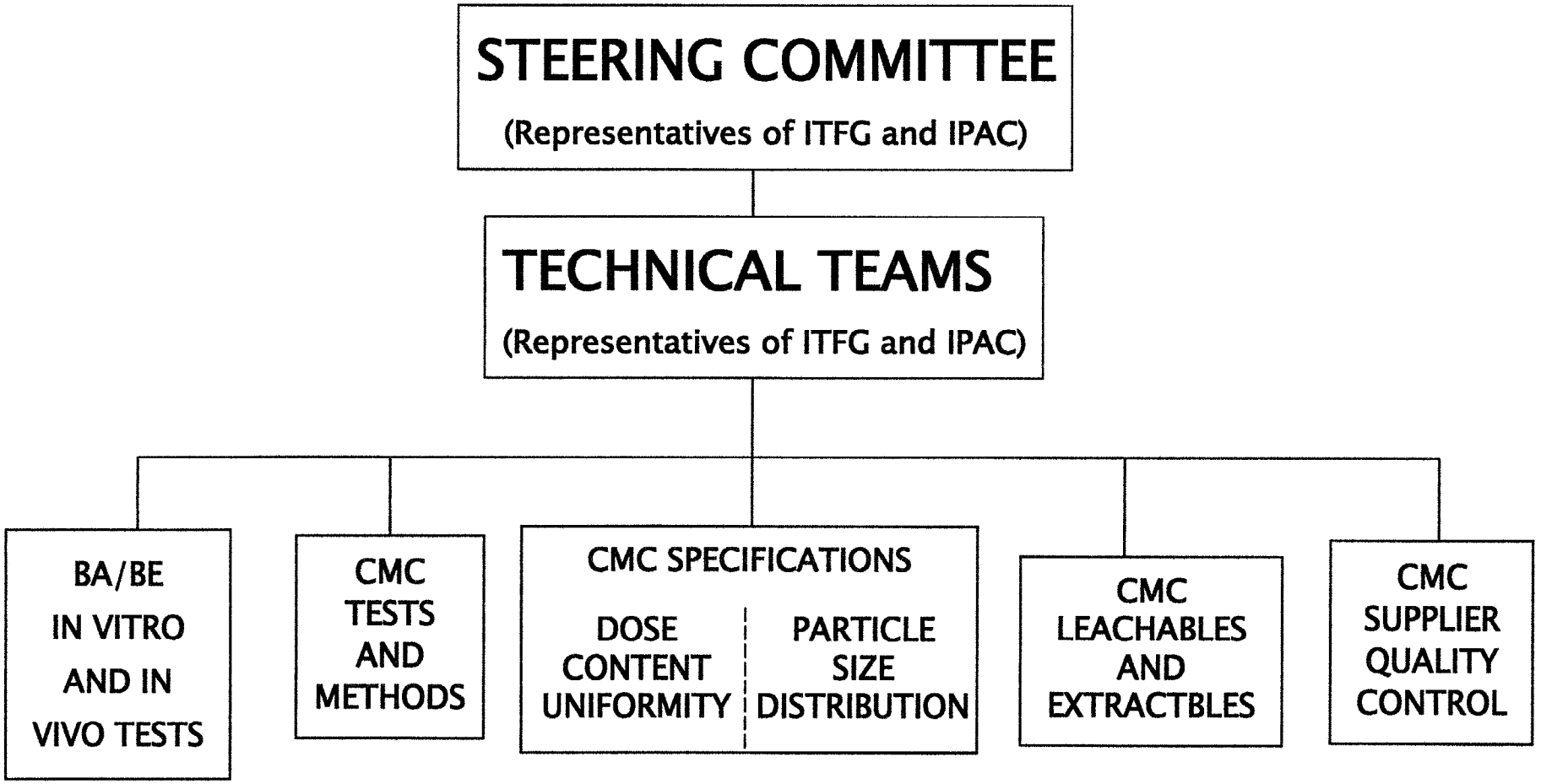
The Collaboration includes the following five Technical Teams:

- **BA/BE In Vitro and In Vivo Tests Technical Team**
- **CMC Specifications Technical Team**
- **CMC Tests and Methods Technical Team**
- **CMC Supplier Quality Control Technical Team**
- **CMC Leachables and Extractables Technical Team**

Technical Teams are in the process of collecting data and scientific information to investigate selected BA/BE and CMC issues in the draft Guidances

Steering Committee provides guidance to Technical Teams and reviews the findings

FRAMEWORK OF ITFG/IPAC COLLABORATION



PARTICIPATION IN THE COLLABORATION

Approximately 85 individuals and more than 20 companies are participating in the ITFG/IPAC Collaboration. Participants are from the following companies/institutions:

3M Pharmaceuticals	Inspire Pharmaceuticals
Agouron	IVAX
Aradigm	Kos Pharmaceuticals
AstraZeneca	Lovelace Respiratory Institute
Aventis	Magellan Laboratories
Bespak	Pfeiffer
BI Roxane	Presspart
Boehringer Ingelheim	Primedica
Dura Pharmaceuticals	Schering-Plough
Eli Lilly	Trudell Medical
Glaxo Wellcome	University of Rhode Island
Inhale Therapeutic Systems	Valois

WORK OF TECHNICAL TEAMS

In separate presentations today, leaders of the ITFG/IPAC Technical Teams will:

- provide an overview of the work of each Technical Team

and

- describe the Collaboration's commitment to contribute constructively to the deliberations of the OINDP Subcommittee and the Agency's development of the OINDP Guidance documents

RECOGNITION OF AGENCY'S COMMITMENT TO IMPROVING QUALITY OF OINDP

- ITFG and IPAC recognize and appreciate the significant effort made by the Agency to issue the draft product quality OINDP Guidances

- ITFG and IPAC strongly support the creation of the OINDP Subcommittee and are pleased to be able to participate in today's meeting

- We thank the Subcommittee and the Agency for considering our comments and proposals

at

AT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ORALLY INHALED AND NASAL DRUG PRODUCTS SUBCOMMITTEE OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Tuesday, April 26, 2000

8:30 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

possible, delineate between these two sets of formulations and make it very clear what testing is required for which one because our fear is that we come to the FDA and we are going to be expected to meet all the requirements for a nasal solution or a respiratory solution and they don't really apply to a buckle solution.

Thank you very much.

DR. LEE: Thank you.

Next comes a series of presentations by two groups that have been very active in this area. Dr. Cummings?

AAPS Inhalation Technology Focus Group (ITFG)/

International Pharmaceutical Aerosol Consortium (IPAC)

Collaboration Technology Teams

Overview of the ITFG/IPAC Collaboration

DR. CUMMINGS: Good afternoon. Thank you for the opportunity to speak today.

[Slide.]

My name is Harris Cummings. I am with Magellan Laboratories and Research at Triangle Park, North Carolina. In the next few minutes, four minutes, I believe, I would like to provide a brief overview of the collaboration between the Inhalation Technology Focus Group and the International Pharmaceutical Aerosol Consortium in addressing the recent draft guidances from the FDA and to express the extent of interest and commitment on the part of

industry to support the further development of these guidelines for inhaled products.

[Slide.]

Two groups are involved in this collaboration, the Inhalation Technology Focus Group which is the focus group of the AAPS is comprised of pharmaceutical scientists concerned with inhalation products.

[Slide.]

Also represented is the International Pharmaceutical Aerosol Consortium which is an association of manufacturers of aerosol products.

[Slide.]

Shown here are the three draft guidances which I think we are all pretty familiar with by now.

[Slide.]

As far as perspective of the two groups, both the ITFG and IPAC are in full agreement as to the value of the new guidance documents and welcome their issuance. In addition, we agree with the BA/BE and statistical issues including the questions surrounding dose content uniformity presented by the subcommittee today.

We do, however, believe that, in addition to these important questions, there are many significant CMC issues particularly related to testing and specifications that still need to be addressed. In addition, we believe that

these difference can and need to be resolved through a data-driven and science-based approach to achieve the best guidances possible, a process which IPAC and ITFG have started and are prepared to continue to support.

[Slide.]

The ITFG/IPAC collaboration was proposed in the IPAC statement at the June '99 workshop as a part of a consensus-building process involving collaboration with the ITFG. The collaborative work between the two groups began in September of 1999.

[Slide.]

The structure of the organization is as shown on the slide and it consists of the steering committee and five technical teams. The steering committee provides general oversight and review for the five technical teams which are shown in the slide and the technical teams are formed based on the general technical subjects found in the three guidances.

As you can see, CMC issues are the primary concern of the documents and of the technical teams.

[Slide.]

The significance of the concern and commitment on the part of industry is also reflected in the number of companies involved in this collaboration. Individuals for more than twenty companies representing a broad spectrum of

industry, including manufacturers, contract organizations and component suppliers participate in this collaboration.

In addition to the approximately 85 individuals who participate directly in the steering committee and technical teams are many times that number of scientists at member companies who work on collection and evaluation of data.

[Slide.]

In the presentations that follow mine, a representative of each of these technical teams will present the current activities of the team and future work which the team plans and the commitments that each team is willing to make to further the work of the subcommittee. This includes generation of data, technical papers and recommendations and even a willingness to meet with the subcommittee, if desired.

[Slide.]

Finally, the pharmaceutical industry, as represented by the IPAC/ITFG collaboration, is committed to a science-based and data-driven process of establishing best practices for the FDA guidances. Large amounts of work have already been completed in this process and even more has been committed to by the member companies of this collaboration.

Thank you very much for your consideration.

DR. LEE: Thank you very much.

The next presentation is on BA/BE by Steve Farr.

Presentation on the Work of the BA/BE Team

DR. FARR: Thank you, Dr. Lee. Good afternoon, ladies and gentlemen>

[Slide.]

I am Steven Farr. I am actually from Aradigm Corporation in Hayward, California. I am grateful for this opportunity to present to you today on behalf of the BA/BE in vitro and in vivo Test Team. Over the course of a number of meetings, the team is about through collection and evaluation of relevant information, a series of data-driven position statements that I wish to share with you today.

While the team used the current draft BA/BE guidance document pertaining to aerosol products for nasal application, it believes the findings are generally applicable to in vitro and in vivo testing of products that are both orally inhaled as well as nasal products.

[Slide.]

In the slide that you have in front of you, it really describes the team's work that has lead to the following propositions. And these were agreed to at the last meeting. With respect to in vitro testing, we strongly agree that it is essential for pharmaceutical product equivalence to have these tests and they should be included

[Slide.]

Based on currently available information, the team has reached the following conclusions. Current in vitro tests, namely dose-content uniformity and particle-size distribution, may be used to estimate lung deposition but their predictability with respect to bioequivalence has not yet been shown.

Furthermore, the in vitro tests described in the current draft guidance are not necessarily more relevant or discriminating than clinical studies for the measurement of bioequivalence. Systemic PK/PD studies will estimate local exposure which will contribute to safety but may not estimate local delivery which will contribute to efficacy and local tolerance.

In turn, efficacy studies alone of a locally-acting agent cannot establish bioequivalence since they will not assure comparable safety through systemic exposure. So, bearing in mind these preceding conclusions, the team believes that in vitro alone are not sufficient to assess product quality for bioequivalence.

Indeed, the guidance should not distinguish between testing requirements for nasal suspensions and solutions for in vivo BE.

[Slide.]

In closing, I just would like to inform the

subcommittee that the team is committed to prepare a technical paper by the end of June this year to support the conclusions described today. The purpose of the paper will be to highlight areas where there is sufficient data to draw conclusions and where there is not enough data at present, and also to review technical documentation related to BA/BE issues addressed by the team.

In addition, the team will be prepared to address the BA/BE questions which have been posed during today's meeting.

Thank you.

DR. LEE: Thank you.

The next up is Dr. Bo Olsson addressing the specifications.

Presentation of the Work of the Specifications Team (Dose Content Uniformity/Particle Size Distribution)

DR. OLSSON: Good morning. My name is Bo Olsson, AstraZeneca. I am grateful for this opportunity to present the statement of the CMC Specifications Technical Team.

[Slide.]

Our focus has been on dose-content uniformity and particle-size distribution as the key attributes. For the industry, internationally harmonized guidelines is the key component for timely and cost-effect development of safe and efficacious drug products. A tremendous amount of work has

gone into establishing a range of harmonized guidelines between the United States, Europe and Japan through the ICH process.

The Technical Team on CMC specifications believes that orally inhaled nasal drug products are amenable to the principles set forth by ICH. Particularly, the ICH Guideline Q6A on specifications provides a process for establishing specifications and the extended application to inhaled dosage forms is being encouraged by the document.

[Slide.]

The ICH Q6A recommends a data-driven process for specification setting. Based on pharmacopeial standards, results from development and from pivotal batches and a reasonable range of analytical and manufacturing variability. We concur with Q6A that it is important to consider all of this information an we don't believe it is justified to apply a single standard specification to the wide range of different products that are on the market and in development.

[Slide.]

Based on the collective experience, the Specifications Team has posed the hypothesis that the current state of OINDP technology may not allow general compliance with the DCU specifications in the draft guidances.

To address this question, to date more than twelve companies have initiated the process to collect a worldwide blinded database of more than 45 products to examine actual DCU capability of these products. Our target is to have an initial assessment of the database by the end of July.

It is our position that the format of specifications should be based on sound statistical practices such that they can be translated into quality requirements. We propose to work with the subcommittee and the agency to investigate using this database, alternate DCU specifications which may better serve this purpose.

This includes those approaches presented by Dr. Walter Hauck this morning.

[Slide.]

Also, for particle-size distribution data, we have initiated a process to collect a database. The target date for initial assessment is, again, by the end of July. The purpose of this survey is primarily to examine the relevancy of the mass balance criterion as a product specification versus a system-suitability requirement. But it may also be used for looking into profile comparison techniques as well.

[Slide.]

In summary, we believe that the achievements of ICH should be taken advantage of in the FDA guidances and we are collecting a wide database which we hope can provide

useful information for the subcommittee and the agency.

Thank you for your attention.

DR. LEE: Thank you.

The next subject is tests and methods. Carole Evans?

ITFG/IPAC Technology Team: CMC Tests and Methods

DR. EVANS: Good afternoon.

[Slide.]

My name is Carole Evans from Magellan Laboratories. My role in this series of presentations is to give an overview of the work and approach of the Test and Methods Team. The team has reviewed the draft CMC guidances and has identified areas where the FDA approach differs from that which we in industry feel is meaningful and scientific justified.

[Slide.]

As a result of this review, we have identified four general concerns. Firstly, while recognizing there are certain key tests which are required for all dosage forms, we feel that the requirement for certain other tests should be driven by a critical review of the data and that the guidance should, therefore, distinguish between these two categories of tests.

In some instances, the language used in the guidance was ambiguous. For example, we are uncertain of

[Slide.]

Our approach has been to develop position statements on each of these areas and the outline of those is provided in our written statement. We plan to collect data with regard to most of these position statements. In cases where the request is simply for rewording or for further harmonization, we will not be collecting data.

[Slide.]

We are currently in the process of collecting the data. This data will allow us to evaluate and, where necessarily, refine our position statements. To date, we have only addressed the guidance with respect to metered-dose inhalers. It is our intent to repeat the process for other dosage forms.

[Slide.]

After we have completed this process, we would like the opportunity to share our recommendations with the subcommittee and the agency. We believe that data-driven recommendations will be helpful to the subcommittee and, ultimately the agency, in creating stronger guidances. We hope we can continue this discussion on critical CMC issues by providing these documents and welcome an opportunity for further dialogue.

Thank you.

DR. LEE: Thank you very much.

Next up is leachables and extractables. Dr. Dave?

Presentation on the Work

of the Leachables And Extractions Team

DR. DAVE: Thank you, Vincent. My name is Kaushik Dave. Actually work for Schering Plough. However, this afternoon, I represent the Extractable and the Leachable Team. What I will present is the opinion of the team based on reviewing the draft guidances.

[Slide.]

The team recognizes the importance of control of extractables and leachables from the point of view of patient safety and quality of these inhalation products. The team is committed to providing information in this area.

[Slide.]

Just to give you some background with regard to definitions, extractables is what one observes when one uses solvents. Leachables is what appears in the product. Just to put it in some other words here, I hope that you can extract as much as you can from this presentation and, from my perspective, I hope a lot of this leaches in.

[Slide.]

Just to share with you; the team has identified four particular areas of focus which are listed up there. The general approach which the team is taking is collecting data from several companies and what we plan to propose to

analysis here, firstly. Secondly, we are trying to compare extractables, which is a solvent-based phenomenon to leachables which is formulation-dependent. Can we really come up with a correlation and what kind of correlation should that be?

What the team proposes to do is, after reviewing data, come up with a working definition of a correlation.

[Slide.]

The third and most important area of discussion in the team is safety qualifications of leachables. We feel that this is an extremely important area where there is a need for discussion and understanding as to what are the requirements. Simple questions like, "What is the criterion for qualification? How do we determine the levels? Does ICH apply here? If it does, do we compare it to the active ingredient. They are not chemically related; does that make sense?"

Again, the team has formed a working group composed predominantly of toxicologists from the industry they will be reviewing this closely and making some recommendations.

[Slide.]

The fourth and final area of discussions in the team is is this the right way of approaching control of components, testing them at the end. Shouldn't we building

quality into components instead of looking for quality at the end? Again, there are a lot of systems out there, quality systems, which would insure that quality components are produced and also those quality systems will include change control and audit.

Actually, we have a technical team, the Supplier QC, which is looking into this.

[Slide.]

Finally, the team is committed to offer databased technical reports and recommendations to the agency and the subcommittee over the course of the next three to four months. Also, secondly, the team is available to evaluate any extractables or leachables issue which the subcommittee or the agency would like us to.

Thank you very much.

DR. LEE: Thank you.

The next issue concerns supplier quality control. Mr. Hansen?

Presentation on the Work

of the Supplier Quality Control Team

MR. HANSEN: Thank you and good afternoon.

[Slide.]

My name is Gordon Hansen from Boehringer Ingleheim Pharmaceuticals. I would like to take the next few minutes to present an overview of the work of the ITFG/IPAC Supplier

Quality Control Supplier Qualification Team. This collaboration has presented a unique opportunity for representatives from the pharma industry and component suppliers to collaborate on a review of the key issues in the draft CMC guidances which relate to the testing and qualification of inhalation-device components and excipients.

[Slide.]

The draft CMC guidances focus extensively on testing of components as well as excipients. A core theme of the CMC guidances with respect to these components is that tight standards and extensive testing by the pharma manufacturer are required in order to assure batch-to-batch quality of components and excipients.

[Slide.]

The team, in reviewing these guidances, has drafted a thesis or vision statement which may be described as follows. The qualification and control of critical components in the area of performance-related physical testing, extractables and leachables and excipients should be achieved by a combination of appropriate scientific practices, cGMP controls and supplier qualification systems.

[Slide.]

The first step for the team was to collect data on current GMP practices. A survey of suppliers was conducted

to evaluate quality and compliance practices at all stages of component, excipient, raw-material and active-substance manufacture. Information was obtained from fifty-three suppliers from raw materials through finished component manufacture.

[Slide.]

The results of the survey are shown on this slide. One is that the level of cGMP awareness and compliance in the component and raw-material supply chain is improving but improvement needs to continue. Secondly, there are specific cGMP program elements which remain to be generally accepted and implemented especially early in the supply chain.

[Slide.]

Some general observations were also made from the survey in that there are no generally accepted cGMP guidelines for the component supply chain but guidelines do exist for the control of bulk excipient manufacturers which have been drafted by IPEC, which is the International Pharmaceutical Excipients Council.

[Slide.]

The team proposes the following: the team endorses the IPEC guideline for the control and cGMP compliance of excipients and it encourages its broader acceptance. The team also proposes that an industry-wide initiative be established to develop a cGMP guideline for component

suppliers. This collaboration would be a unique, perhaps unprecedented, partnership between suppliers, the pharma industry and the agency in designing a system which assures product quality by building it in rather than by extensive testing by the end user.

[Slide.]

The team also requests that the agency partner with the pharma industry and component suppliers by first formally recognizing the value of the cGMP guideline for component suppliers by acknowledging in the guidance documents that if sufficient supplier mechanisms are in place, appropriate reductions in testing will be considered.

We also ask that the agency help establish key elements and expectations for the cGMP guideline for components and participates in reviewing and commenting on draft guidelines.

Thank you for your time.

DR. LEE: Thank you.

Now comes the concluding presentation by this group, Cynthia Flynn.

Concluding Presentation on ITFG/IPAC Collaboration

DR. FLYNN: Good afternoon.

[Slide.]

My name is Cynthia Flynn. I work for Aventis Pharmaceuticals. I would like to take this opportunity to

review very briefly the deliverables which the technical teams are committed to providing and the time frames associated with those deliverables. Firstly, the BA/BE team is committed to preparing a technical paper on BA/BE that have been highlighted in the previous presentation. This will be completed by the end of June.

In addition, that team will attempt to address as many questions as possible as have been raised during this meeting.

The Specifications Team is committed to completing, by the end of July, an initial statistical assessment of the actual DCU and particle-size database which is collected by this collaboration. We would very much like to share this initial assessment with you and with Dr. Hauck in order to help your endeavors.

The Test and Methods Team is committed to completing, within the next three to four months, the technology paper outlining the key MDI tests. In addition, in the future, we also plan to do similar work for other dosage forms, as was alluded to by Carole in the previous presentation.

The Leachables and Extractables Team is committed to also completing a technical report within the next three to four months as well as to making recommendations within the next three to four months concerning leachables and

extractables.

Lastly, the Supplier Quality-Control Technical Team is volunteering to ask as a co-leader with the agency in developing a cGMP guideline for component manufacturers.

[Slide.]

I would like to point out to the committee that it should be noted that the work of the collaboration deals with not only BA/BE issues, which have received substantial emphasis today, but also places a significant amount of emphasis on four critical CMC issues, not just the DUC issue.

[Slide.]

The collaboration of ITFG/IPAC is very convinced of the need for a science-based interactive dialogue and is requesting that the agency continue the subcommittee process. We are also requesting that the collaboration be given the opportunity to provide the deliverables that I just described in the next three to four months for the use of the subcommittee and agency in order to assist in the resolution of the various CMC, BA/BE issues.

[Slide.]

I would like, then, to conclude my remarks by acknowledging several groups. First of all, we would like to express our deep gratitude to the agency for holding this meeting and allowing us to present the work that has been

will develop or deliver will be a consensus document?

DR. FLYNN: Correct.

DR. LEE: Thank you.

That concludes the presentations by those two groups. Now we have two more to go. Next up is on CMC issues by Dr. Neugebauer.

CMC Issues

DR. NEUGEBAUER: My name is Ken Neugebauer. I am the Director of Marketing for Solvay Fluorides responsible for the NAFTA region. I am speaking on behalf of and presenting the comments of Ms. Anja Pischtiak, Product Manager of Pharmaceutical Aerosols for Solvay Fluor based in Hanover, Germany.

[Slide.]

Solvay Fluor is a manufacturer of the propellants HFA227 and HVA134a used in inhalation drug products, marketed by Solvay under the trade name of Solkane, would like to make two comments on the major excipients and MDIs, the noncompendial propellants 227 and 134a. The comments relate to the draft guidance for industry, metered-dose inhaler and dry-powder inhaler drug products chemistry, manufacturing and controls documentation.

[Slide.]

The first point. Lines 288 to 295 identify a requirement for a toxicological qualification of the novel

excipients 134a and 227 but do not give directives of what comprises a toxicological qualification. The consortia IPACT I and II have submitted to the FDA extensive safety data on 134a and 227 intended for inhalation which may sufficiently demonstrate the toxicological suitability of the novel excipients 134a and 227 for use in medical products including MDIs.

Solvay believes that the uncertainty of the requirements for a toxicological qualification of the pure excipients strongly inhibits the pharmaceutical industry from reformulating its CFC-containing products to HFAs. Therefore, we propose that a definition for the toxicological qualification of the noncompendial propellants HFA134a and HFA227 be added to the draft.

The second point we want to make, lines 381 to 405 show impurity acceptance-criteria limits for 134a impurity by impurity, which are given in such detail, strictly process related. Solvay, for example, uses for the manufacturer of 134a pharma a process starting from trichlorethylene which is not mentioned in the FDA specification.

However, it is present in trace, but detectable, amounts in our product and, therefore, is specified by Solvay. While Solvay has four additional impurities not shown in the specification quoted by the FDA, sixteen other

impurities that are listed in the draft specifications are not contained in Solkane 124a as manufactured by Solvay.

Therefore, Solvay proposes to replace detailed impurity-by-impurity limits with acceptance criteria based on toxicological tests performed both for HFA134a and for HFA227.

[Slide.]

I submit, with these comments, Solvay's specification--that is impossible to read; I apologize. I will get a clearer copy for publication. Basically, this is our specification for 134a with detailed description of all of the impurities listed and comparison for what Solvay manufactures in the draft guidance.

[Slide.]

This slide is the specification for Solkane 227 pharma as filed currently with the FDA to be added to the draft guidance in case the 134a specification remains. The 227 specification is currently omitted.

Finally, I have included with my submission that we agree in principle with comments previously submitted by IPACT as published in the August 1999 Gold Sheet. Again, I am submitting them with the key points highlighted for the committee.

Thank you very much.

DR. LEE: Thank you very much.

sensitive assays that are being developed, we do have an ability to measure or detect plasma concentrations after oral inhalation in nasal products although we do have some cases where we are still struggling with the measurement of these plasma concentrations, or detecting and quantifying these concentrations.

So I would actually say that we do require that pharmacokinetic-based bioavailability studies be conducted, both to understand from a clinical pharmacology perspective as well as the product-quality perspective. However, for orally inhaled and nasal drug products intended for local action, it is multiple aspects that have to be address. Bioavailability and bioequivalence cannot be solely addressed based on pharmacokinetics.

But, because of the accuracy and, wherever possible, we say pharmacokinetic studies are the first choice to characterize the systemic exposure. However, that alone is not sufficient. You need additional pharmacodynamic data from a safety perspective as well as clinical efficacy data where appropriate.

Thank you.

DR. LEE: Thank you very much.

Dr. Harrison, you have the last words, but you only have twenty minutes.

Industry View

DR. HARRISON: Good afternoon. I want to thank you for allowing me to be the last presenter.

[Slide.]

My topic is PK and PD studies for systemic exposure of locally acting drugs. I am giving an industry viewpoint.

[Slide.]

The value of PK for OINDP is that it measures systemic absorption or systemic exposure. Both terms are used in the guidance. I look at them as interchangeable. Really, what they are doing is measuring systemic safety. PK is an established bioequivalence metric. It can be standardized. It can be validated. It is discriminating. So certainly it has an awful lot of pluses for it.

[Slide.]

There are some concerns, however, with PK that were raised. One is the low doses that are given nasally and by inhalation, what limitations that imposes. The assay lower limit of quantitation; there is quite a bit of variability that is encountered in PK studies for the nose. There could be draining of excess dose so that you really don't get a good dose response. And, for oral inhalation, the dosing technique is quite critical.

[Slide.]

What I want to do is address those concerns up

The final speaker of this session is on growth effects of nasal steroids by Dr. Schenkel.

Growth Effects of Nasal Steroids in Children and Differences among the Steroid Preparations

DR. SCHENKEL: Good afternoon. I want to thank the committee for allowing me to speak about this issue.

[Slide.]

I am a practicing allergist. I am Director of Valley Clinical Research Center in Easton, Pennsylvania. I have been involved in a number of clinical trials looking at differences among the various nasal corticosteroids. What I am going to be talking about in the next few minutes is exactly that, the differences among the steroids in a clinical setting.

You have heard a lot today about trying to look at in vitro models and how to tell differences among the steroids. I am going to point out to you the fact that there are differences, not just in bioequivalence but in what I have called bioactivity, particularly in the pediatric population and particularly the effects on growth.

I would urge the subcommittee to look at this very carefully. It has already been looked at by the FDA in terms of acknowledging a new pediatric labeling for nasal corticosteroids.

It is well known that oral corticosteroids can